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ETIOLOGY OF ATYPICAL ("VIRUS") PNEUMONIAS

WITH A BRIEF RÉSUMÉ OF RECENT DISCOVERIES

HOBART A. REIMANN, M.D.

W. PAUL HAVENS, M.D.

AND

ALISON H. PRICE, M.D.

PHILADELPHIA

During the past few years an increasing amount of attention has been given to a pneumonic syndrome which differs sharply from pneumococcic lobar pneumonia and from other familiar pneumonias of known causation. It has occurred in two general forms, one represented by a small proportion of cases of pneumonic involvement in epidemics of mild disease of the respiratory tract, like those cases described by Bowen,[1] Allen [2] and most other authors, and the other represented by isolated, sporadic, nonseasonal cases of severe disease, occurring chiefly in persons over 30 years of age. In the former the incubation period appears to be a matter of a few days, and in the latter it is longer, up to two weeks or more. Both forms are characterized by a gradual onset with dry inflammation of parts or all of the mucosa of the respiratory tract; chills or chilliness; slowly rising fever lasting one to three weeks and falling by lysis; delayed signs of migratory pneumonia, often bilateral; relative bradycardia; unproductive cough; headache; photophobia; sweating, and a normal leukocyte count. Therapy with sulfonamide compounds has no influence on the course of the disease; complications are rare, and the mortality rate is practically nil. Because of inability to associate any bacteria with the disease and because of epidemiologic, clinical and pathologic resemblances to certain pneumonias caused by filtrable viruses, a virus was surmised to be the cause,[3] and the term "virus" pneumonia came into common usage. Some persons prefer to

From the Department of Medicine, Jefferson Medical College Hospital.

1. Bowen, A.: Acute Influenza Pneumonitis, Am. J. Roentgenol. **34**:168-174 (Aug.) 1935.

2. Allen, W. H.: Acute Pneumonitis, Ann. Int. Med. **10**:441-446 (Oct.) 1936.

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call the disease "atypical" pneumonia, which seems too vague, since any pneumonia not conforming to the typical lobar form is atypical. Such an ambiguous term as "typical atypical" pneumonia has already been employed. Many other clinically and anatomically descriptive names have been used, as is evident in the titles of the appended references, but until its apparent diverse origin is discovered, confusion in classification must be expected.

During an epidemic of mild disease of the respiratory tract in the winter of 1939-1940 [4] a small number of cases of a severe form were encountered at the Jefferson Medical College Hospital, and the condition was tentatively regarded as "virus" pneumonia because of a similarity to the severe nonseasonal, sporadic disease observed the year before.[3] However, in 1941 and 1942 26 more cases of isolated, sporadic, nonseasonal disease occurred, which on epidemiologic grounds suggests that the etiologic agent of the epidemic form and that of the sporadic form may be different. In the last two years we have encountered 4 cases in October, 5 in December, 8 in January, 3 in February, 2 in March, 2 in April and 2 in May. The total number comprised about 15 per cent of all cases of primary pneumonias studied in the hospital in the same years.

Since "virus" pneumonia is rarely fatal in adults, only 2 necropsy reports on patients regarded as having the disease are available. In both instances [5] the histologic reaction in the lungs was composed chiefly of mononuclear cells, and no bacteria were present. This cellular response occurs in pneumonias caused by known filtrable viruses and, together with the presence of cytoplasmic inclusion bodies in the lungs of infants dying from a form of "virus" pneumonia,[6] supports the concept of virus causation. On the other hand, a similar histologic reaction is evoked by Haemophilus pertussis, Pasteurella tularensis, Toxoplasma, toxins and irritative chemicals, so that opinion cannot be based on pathologic changes alone.

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3. (*a*) Reimann, H. A.: An Acute Infection of the Respiratory Tract with Atypical Pneumonia: A Disease Entity Probably Caused by a Filtrable Virus, J. A. M. A. **111**:2377-2384 (Dec. 24) 1938. (*b*) Reimann, H. A., and Stokes, J., Jr.: Epidemic Infection of the Respiratory Tract in 1938-1939: A Newly Recognized Entity, Tr. A. Am. Physicians **54**:123-127, 1939.

4. Reimann, H. A., and Havens, W. P.: An Epidemic Disease of the Respiratory Tract, Arch. Int. Med. **65**:138-150 (Jan.) 1940.

5. Kneeland, Y., and Smetana, H. F.: Current Bronchopneumonia of Unusual Character and Undetermined Etiology, Bull. Johns Hopkins Hosp. **67**:229-267 (Oct.) 1940. Longcope, W. T.: Bronchopneumonia of Unknown Etiology (Variety X): A Report of Thirty-Two Cases with Two Deaths, ibid. **67**:268-305 (Oct.) 1940.

6. Adams, J. M.; Green, R. G.; Evans, C. A., and Beach, N.: Primary Virus Pneumonitis: A Comparative Study of Two Epidemics, J. Pediat. **20**:405-420 (April) 1942.

Our only fatality in 1941-1942 occurred in a woman aged 49, who died on the twenty-second day of illness. Chronic pyelonephritis, acute focal hepatitis and bilateral pneumonia were encountered post mortem. Histologically, the alveolar exudate was uncharacteristic, consisting predominantly of polymorphonuclear cells, and an occasional alveolus was lined with a hyaline membrane. No bacteria were seen in stained sections from the pneumonic areas, and cultures from various areas were sterile.

ETIOLOGIC STUDIES

Since the first etiologic studies on the problem were made in 1938 [3] a surprising array of diverse agents were found to cause the syndrome called "virus" pneumonia, but in most cases attempts to isolate a filtrable virus from blood, secretions and the lungs have failed. In the first trials a filtrable agent was recovered from 2 patients but was lost in animal passage before its etiologic relation could be tested.[7] Martin and Fairbrother [8] reported a similar experience. Weir and Horsfall [9] isolated a virus virulent for mongooses from patients with a disease ostensibly "virus" pneumonia. The virus was specifically neutralized by convalescent serum from infected animals and also by serum from the patients from whom the virus appeared to have come.

In 1938 Francis and Magill [10] reported the isolation of an unusual virus from patients with an influenza-like disease. The virus caused meningitis and pneumonia in inoculated animals and was named the virus of meningopneumonitis. Retrospective tests on some of the patients gave indirect evidence that they had been infected with the virus of influenza B. It is therefore uncertain whether the virus of meningopneumonitis came from the patients and was etiologically related to their disease or whether it was of animal origin. The authors pointed out the resemblance of the virus to the viruses of lymphogranuloma venereum, psittacosis, lymphocytic choriomeningitis and Theiler's encephalomyelitis of mice.

Eaton, Beck and Pearson [11] studied a localized outbreak of 6 cases of severe atypical pneumonia, 3 of them fatal. In 4 cases a virus was isolated which was similar to, yet not identical with, the virus of

7. Stokes, J., Jr.; Kenney, A. S., and Shaw, D. R.: A New Filtrable Agent Associated with Respiratory Infections, Tr. & Stud., Coll. Physicians, Philadelphia **6**:329-333 (Feb.) 1939.

8. Martin, A. E., and Fairbrother, R. W.: An Epidemic of Apparent Influenza, Lancet **2**:1313-1315 (Dec. 23) 1939.

9. Weir, J. M., and Horsfall, F. L., Jr.: The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose, J. Exper. Med. **72**:595-610 (Nov.) 1940.

10. Francis, T., Jr., and Magill, T. P.: An Unidentified Virus Producing Acute Meningitis and Pneumonitis in Experimental Animals, J. Exper. Med. **68**: 147-160 (Aug.) 1938.

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psittacosis. Curiously, this new psittacosis-like virus is also related to, or is identical with, the virus of meningopneumonitis, as shown by reciprocal complement fixation and active immunity tests in mice. A subsequent report by Rake, Eaton and Shaffer [12] added another unsuspectedly related virus to the group, namely, that of lymphogranuloma venereum. Each of these viruses—that of psittacosis, of a psittacosis-like infection, of meningopneumonitis and of lymphogranuloma venereum—causes meningitis, pneumonia and granulomatous infiltrations in the skin in experimental animals. The lesions in each infection are microscopically indistinguishable. Furthermore, serum from numerous patients with atypical pneumonia fixed the antigens of meningopneumonitis, psittacosis and lymphogranuloma venereum, and a cutaneous test with antigen of the last-named disease (the Frei test) gave positive results in 5 of 8 cases.[13] This evidence of striking immunologic relation of the four viruses, together with their morphologic and tinctorial resemblances, suggest that the viruses belong to a closely related group and may have originally arisen from a parent strain, probably residing in animals or birds, which subsequently has become diversified by passage and adaptive residence in different hosts and tissues.[13]

Of further interest in this respect is the occurrence of "fulmar" psittacosis apparently contracted from marine birds, as reported from Scandinavia,[14] of the isolation by Pinkerton and Swank [15] of another psittacosis-like virus from pigeons and the report of a case of probable psittacosis thought to have been contracted from pigeons.[16]

Meyer, Eddie and Yanamura [17] isolated the virus of a psittacosis-like disease from the lung of a patient who had been in contact with pigeons,

11. Eaton, M. D.; Beck, M. D., and Pearson, H. E.: A Virus from Cases of Atypical Pneumonia: Relation to the Viruses of Meningopneumonitis and Psittacosis, J. Exper. Med. **73**:641-654 (May) 1941.

12. Rake, G.; Eaton, M. D., and Shaffer, M. F.: Similarities and Possible Relationships Among Viruses of Psittacosis, Meningopneumonitis, and Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **48**:528-531 (Nov.) 1941.

13. Eaton, M. D.; Martin, W. P., and Beck, M. D.: The Antigenic Relationship of the Viruses of Meningopneumonitis and Lymphogranuloma Venereum, J. Exper. Med. **75**:21-33 (Jan.) 1942.

14. Rasmussen, R. K.: Ueber eine durch Sturmvögel übertragbare Lungenerkrankung auf den Faröern, Zentralbl. f. Bakt. (Abt. 1) **143**:89-93 (Dec. 30) 1938.

15. Pinkerton, H., and Swank, R. L.: Recovery of a Virus Morphologically Identical with Psittacosis from Thiamin-Deficient Pigeons, Proc. Soc. Exper. Biol. & Med. **45**:704-706 (Nov.) 1940.

16. Alicandri, H.: Psittacosis, J. A. M. A. **118**:1214 (April 4) 1942.

17. (*a*) Meyer, K. F.: Pigeons and Barn Yard Fowls as Possible Source of Human Psittacosis or Ornithosis, Schweiz. med. Wchnschr. **71**:1377-1379 (Nov. 1) 1941. (*b*) Meyer, K. F.; Eddie, B., and Yanamura, H. Y.: Ornithosis (Psittacosis) in Pigeons and Its Relation to Human Pneumonitis, Proc. Soc. Exper. Biol. & Med. **49**:609-615 (April) 1942.

many of which also proved to be infected with the same virus. Another patient apparently contracted the disease from infected chickens.[18] Meyer named the disease ornithosis to distinguish it from infection peculiar to psittacine birds.

Smadel and his associates [19] studied 2 unusual fatal cases of lymphocytic choriomeningitis, in both of which patchy pneumonic areas composed largely of mononuclear cells were present. In 1 case pneumonia was the sole lesion encountered post mortem. During the illness there was evidence of infection of the respiratory tract, but no clinical diagnoses could be made. The causative virus was isolated from the blood, the lungs and brain tissue.

Other recently discovered infections characterized by atypical pneumonia which clinically may resemble "virus" pneumonia are Q fever,[20] coccidioidomycosis [21] and toxoplasmosis,[22] yet the agents causing them are not viruses and seem unlikely to have been the cause of the widespread infection called "virus" pneumonia.

The possible relation of the psittacosis virus or the virus of a psittacosis-like infection (ornithosis) to the condition described as "virus" pneumonia is of great interest. It may be recalled that psittacosis was strongly considered in differential diagnosis in most of our cases [3] and also in the cases reported by other authors.[23] Complement fixation tests for psittacosis were [24] therefore made by Miss Margaret Wall, of the Hospital of the Rockefeller Institute, under the direction of Dr. Joseph E. Smadel, on serum from 8 recently ill patients and from several of those described in previous reports. The test gave a positive result in the following 4 instances.

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18. Meyer, K. F., and Eddie, B.: Spontaneous Ornithosis (Psittacosis) in Chickens the Cause of a Human Infection, Proc. Soc. Exper. Biol. & Med. **49**:522-525 (April) 1942.

19. Smadel, J. E.; Green, R. H.; Paltauf, R. M., and Gonzales, T. A.: Lymphocytic Choriomeningitis: Two Human Fatalities Following an Unusual Febrile Illness, Proc. Soc. Exper. Biol. & Med. **49**:683-686 (April) 1942.

20. Dyer, R. E.; Topping, N. H., and Bengston, I. A.: An Institutional Outbreak of Pneumonitis: II. Isolation and Identification of Causative Agent, Pub. Health Rep. **55**:1945-1954 (Oct. 25) 1940.

21. Farness, O. J.: Coccidioidomycosis, J. A. M. A. **116**:1749-1752 (April 19) 1941.

22. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: A Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, J. A. M. A. **116**:807-814 (March 1) 1941.

23. Dochez, A. R., in discussion on Reimann and Stokes,[3b] pp. 127-128. Maxfield, J. R.: Atypical Pneumonia with Leukopenia, Texas State J. Med. **35**:340-346 (Sept.) 1939. Enders, J. F.: Psittacosis: Virus and Rickettsial Disease, Cambridge, Harvard University Press, 1940, pp. 529-554.

24. Meyer, K. F., and Eddie, B.: The Value of the Complement Fixation Test in the Diagnosis of Psittacosis, J. Infect. Dis. **65**:225-233 (Nov.-Dec.) 1939.

CASE 1.—F. C., aged 50, had a severe shaking chill which lasted about twenty-five minutes on Dec. 20, 1941. Her temperature was then 38 C. (100 F.) and the leukocyte count 10,000. She was given a course of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) therapy by her own physician, without effect. Later the temperature varied between 39 and 40 C. (102 and 104 F.). There were dry, hacking, paroxysmal cough and profuse sweats requiring change of bed clothing. Chills recurred on three further occasions.

The patient came to the hospital on the fifteenth day of illness, with high fever, malaise and cough. She appeared to be moderately sick; the temperature was 39.5 C. (103 F.), the pulse rate 95 per minute and the respiratory rate 24 per minute. Besides an unusual redness of the oral mucous membrane, a few tender cervical lymph nodes and a small area in the right mammary region where a few seemingly unimportant rales were heard, there were no helpful diagnostic features. The leukocytes numbered 6,800; the sedimentation rate was rapid, 34 mm. in twenty-five minutes, and a blood culture was sterile. Tentative diagnoses of typhoid fever, tuberculosis and rheumatic fever were made. On the following day roentgen study showed a surprisingly large dense homogeneous shadow in the lower portion of the upper lobe of the right lung, suggesting lobar pneumonia. No abnormal physical signs were heard over this area, and without roentgen study the extensive involvement would have been overlooked.

The temperature persisted at a high level of 39.5 to 40 C. (103 to 104 F.) until the twenty-second day of illness, when each successive swing was lower, and finally it became normal on the twenty-ninth day. The pulse rate remained fairly constant at 100 per minute. The respiratory rate rose from 22 to 30 per minute on the twenty-second day. Profuse sweating occurred the following day. The highest leukocyte count was never over 10,000 and was without an unusual proportion of cells. Headache was severe during the second week, but there was only an occasional slight cough, without sputum, in spite of the striking shadows in the lung. Subsequent roentgenograms showed a further spread, then a melting, of the density in the upper lobe of the right lung, and on the twenty-third day the whole lower lobe became clouded, but never as densely as the upper lobe. The shadows disappeared four weeks after the onset of the disease. No abnormal physical signs except fine rales in the right mammary and axillary areas and at the base of the right lung posteriorly were ever heard.

A Frei test made on the seventh day of convalescence with lymphogranuloma venereum antigen prepared both from chick embryo and from mouse brain yielded negative results. The results of complement fixation tests for psittacosis were positive in the following dilutions: twenty-third day after the onset of illness, 1:8; thirty-fifth day, 1:32; eighth week, 1:256, and twelfth week, 1:128.

The results of the complement fixation test suggest that the patient was infected with the virus of psittacosis, of a psittacosis-like disease (ornithosis) or of meningopneumonitis.

CASE 2.—C. O., aged 45, went to bed with a "head cold" and malaise about Dec. 13, 1941. He failed to improve and on the third day began to cough and have chilly sensations. Headache was severe. Repeated examinations of the chest failed to reveal abnormal signs until the sixth day, when rales were heard in the lower lobe of the right lung. The patient was admitted to the hospital on the ninth day of illness, with the diagnosis of "virus" pneumonia. There were paroxysmal, unproductive cough and slight dulness and rales in the lower lobe of the right lung. The temperature was 40 C. (104 F.); the pulse rate averaged 90 per minute, and the respiratory rate was 25 per minute. There was no sputum to examine, and a smear

and a culture of the pharyngeal exudate revealed nothing of importance. The leukocytes numbered 8,000 per cubic millimeter.

There were several profuse sweats; the temperature after another peak at 40 C. (104 F.) declined gradually and reached normal on the fifteenth day of illness. Convalescence was uneventful. Serum taken on the twenty-fourth day of illness gave a positive complement fixation reaction for psittacosis in a dilution of 1:128. Serum taken nine weeks later gave a positive reaction in a dilution of 1:64. The result of the Frei test was negative.

CASE 3.—M. T., aged 59, "caught cold" about April 8; the condition was insignificant at first, but the temperature gradually rose to 40 C. (104 F.) after several days, accompanied by headache, chilly sensation, malaise, slight cough and pain in the right side of the chest. She was treated at home with sulfadiazine, without improvement. The cough became worse but unproductive. There were attacks of profuse perspiration. The patient was admitted to the hospital on the fourteenth day of illness. She was not in distress but was slightly cyanotic and dyspneic. The conjunctivas and the pharynx were injected. There were slight dulness and many fine rales in the right scapular and axillary regions. A roentgenogram showed a corresponding area of density, which later enlarged in size. The leukocytes numbered 8,000, 12,000, 7,000 and 11,000 on four occasions. The sedimentation rate was rapid, 30 mm. in forty-five minutes. The temperature of 40 C. (104 F.) on admission dropped gradually to 37.5 C. (99.5 F.) on the twenty-second day of illness, where it remained for another ten days before becoming normal. Clinical improvement occurred on the twenty-second day. Mice inoculated with a small amount of sputum survived more than six weeks.

Blood taken on the sixteenth and the thirty-fifth day of illness gave a positive complement fixation reaction for psittacosis in a titer of 1:64.

CASE 4.—L. M., a Negro aged 26, became sick on Jan. 10, 1941 with a chill followed by nonproductive cough, fever, pain in his chest and profuse sweating. His nose was obstructed; his eyes were red and painful, and there was slight pharyngitis. The symptoms became worse, with headache and dyspnea. A slight amount of sputum was raised. He entered the hospital on the fifth day of disease with a temperature of 40.3 C. (104.5 F.), a pulse rate of 110 per minute and a respiratory rate of 25 per minute. There were slight dyspnea, conjunctival injection, photophobia and a macular eruption on the face, the backs of the hands and arms and the body. The eruption disappeared in a day or two. The pharynx and the tonsils were inflamed, and the submaxillary and the anterior cervical lymph nodes were slightly enlarged and tender. The breath sounds in the base of the left lung and the apex of the right lung were harsh, and only a few rales were heard in the base of the left lung after cough. The abdomen was normal. A roentgenogram of the chest showed a great increase in the density of the hilar markings extending into the periphery of both lungs, with patchy areas of mottled density suggesting pneumonia superimposed on acute tracheobronchitis. Three leukocyte counts varied between 4,300 and 4,700. The sedimentation rate on two occasions was increased and reached 25 mm. in two hours. A blood culture was sterile, and the Wassermann reaction of the blood was negative. Repeated examination of the sputum showed only the usual flora to be present. Mice inoculated intraperitoneally with sputum all survived.

On the sixth day of illness rales were heard in scattered areas in both lungs. The temperature fell during the next few days and reached normal on the tenth day. Blood serum taken on the seventh and the twentieth day after the onset of disease and tested by Dr. Charles Armstrong gave strong protection against the

virus of lymphocytic choriomeningitis. Eleven months later neutralizing antibodies were still demonstrable by Dr. Smadel. Blood serum tested ten and twelve months after recovery also gave positive complement fixation for the virus of psittacosis in a dilution of 1:64.

Complement fixation tests for psittacosis were made on serum from the patients in cases 1, 3 and 9 of the 1938 series,[3] and from the patients in the case described in figure 6 and in 1 other case of the 1939 series.[4] All results were negative. The results are, of course, inconclusive because of the intervals of four and three years since the disease occurred.

COMMENT

In spite of the striking clinical similarities of a certain condition called "virus" pneumonia to psittacosis, even including in some instances mild neurologic symptoms, epistaxis and an exanthem; the sporadic nature of the disease, and the age group principally involved, it is impossible to classify it as psittacosis according to accepted criteria.[25] The chief differences are the evidence in some instances of "virus" pneumonia of person to person contagion, no contact with psittacine birds, the low mortality rate and the failure to isolate a virus.

In none of the 4 cases reported here, in which serum gave a positive complement fixation reaction for psittacosis, was there evidence of contact with known carriers of psittacosis or ornithosis, including pigeons, barnyard fowl or other pet birds, and contact with rats or mice was unlikely except in case 4. The patients could not recall exposure to persons sick with a disease of the respiratory tract prior to their own illness and did not transmit obvious infection to others. All mice routinely inoculated intraperitoneally with nasopharyngeal secretion to detect the presence of pneumococci lived more than fourteen days. Had the virus of psittacosis been present they would probably have died from the infection within this period, according to the test proposed by Rivers and Berry.[26]

The presence of complement-fixing antibodies for psittacosis in these cases is nevertheless of importance, particularly in cases 1 and 2, in which the titer rose and fell during early convalescence. The result in case 3 is less convincing, since the titer did not diminish during convalescence, and in case 4 the tests were made so long after the disease. The negative results of tests on the serum of patients who had pneumonia in 1938 and 1939 are of no significance because of the long time elapsed. Furthermore, the incidence of complement-fixing anti-

25. Rivers, T. M.: Psittacosis, in Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1940, p. 66.

26. Rivers, T. M., and Berry, G. P.: A Laboratory Method for the Diagnosis of Psittacosis in Man, Proc. Soc. Exper. Biol. & Med. **29**:942-944 (May) 1932.

bodies for psittacosis in the general population is unknown. Nevertheless, when positive results are obtained in 4 of 8 cases, they would seem to represent more than a fortuitous occurrence.

The positive results, as discussed previously, only suggest that one of the viruses of psittacosis, a psittacosis-like disease (ornithosis), meningopneumonitis and lymphogranuloma venereum may have been implicated, but in view of the evidence produced by other investigators and positive results in 4 of 8 cases it is likely that one of them was causally related to the disease in question. It is also apparent that these viruses are much more widely distributed in nature than heretofore believed.[17a] Instances of contact infection in our own studies and in those of other investigators suggest that human beings may also serve as reservoirs of infection.

The presence of strong neutralizing properties for the virus of lymphocytic choriomeningitis in the serum of the patient in case 4, in addition to complement-fixing bodies for the virus of psittacosis, is of interest in view of the recent report of Smadel and his associates [19] and the observation of Francis and Magill.[10] But here again, without actual isolation of the first-named virus it is not possible to claim causal relation of it to "virus" pneumonia on this basis alone because of the possibility of an anamnestic reaction and because specific neutralizing bodies are encountered in 10 per cent of normal persons.[27] Furthermore, the possible reciprocal relation between this virus and those of the psittacine group is not yet known.

From the studies mentioned and from the facts at hand the adoption of the term "virus" pneumonia is justified, but only to indicate a syndrome composed of a group of entities, each caused by a specific filtrable virus, as for example, that of psittacosis and related infections, of influenza, of chickenpox,[28] smallpox or of lymphocytic choriomeningitis or perhaps the mongoose-infecting virus. Furthermore, certain agents other than viruses, like the Rickettsia of "Q" fever, the protozoan Toxoplasma and the fungus Coccidioides immitis, may also cause disease resembling the pneumonias caused by viruses. And lastly there is a large group of atypical pneumonias of which the cause is still unknown. Therefore, etiologic studies should be made in all cases of pneumonia, including the special serologic tests for lymphocytic choriomeningitis and for diseases caused by the psittacine group of viruses, and the disease named according to its etiologic agent whenever possible.

27. Armstrong, C.: Studies on Choriomeningitis and Poliomyelitis, in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1940-1941, vol. 36, pp. 39-65.

28. Waring, J. J.; Neubuerger, K. T., and Geever, E. F.: Severe Forms of Chickenpox in Adults, with Autopsy Observations in Case with Associated Pneumonia and Encephalitis, Arch. Int. Med. **69**:384-408 (March) 1942.

CONCLUSION

The term "virus" pneumonia is established to include a syndrome or a group of entities which may be clinically indistinguishable yet may be caused by a variety of known filtrable viruses. Clinically similar instances of pulmonary infection may be caused by known agents other than filtrable viruses, and numerous pneumonias occur in which the causative agent has not yet been determined. The latter at present had best be termed primary atypical pneumonia, etiology unknown.[29]

Indirect evidence of infection with psittacosis virus or the related viruses of a psittacosis-like disease (ornithosis), meningopneumonitis and lymphogranuloma venereum was obtained by complement fixation tests in 4 of 8 cases of a condition regarded as "virus" pneumonia. In 1 case the serum also gave strong protection against the virus of lymphocytic choriomeningitis. Any one of these viruses may be the cause of a form of virus pneumonia.

Jefferson Medical College Hospital.

29. Primary Atypical Pneumonia: Etiology Unknown, Official Statement, War Med. **2**:330-333 (March) 1942.

OBSERVED COURSE OF DIABETES MELLITUS AND INFERENCES CONCERNING ITS ORIGIN AND PROGRESS

ARTHUR R. COLWELL, M.D.
EVANSTON, ILL.

This report presents evidence in favor of the idea that the course of diabetes mellitus begins at birth, that inherent features predetermine the average rate of its progress, that its course is approximately half run before the disease is even recognized and that some years after recognition it may show progressive and permanent improvement. The data which permit these inferences may be obtained by a comparison of the amount of insulin required with the length of time the disorder has existed in comparable groups of diabetic subjects.

The course of diabetes mellitus is variable but is usually related to the age at which the disease appears. This fact is recognized by all clinicians who treat much diabetes. As expressed by Woodyatt,[1] "As a general rule . . . the greater the age at which diabetes appears the slower will be its subsequent course." Exceptions occur at all ages, but the usual course is rapid progress after it begins in early life and more benign behavior when it begins late.

Prior to the discovery of insulin this tendency was reflected in the early death of diabetic children. For example, before 1922, when insulin became generally available, 208 of Joslin's young patients in whom diabetes developed in childhood or adolescence lived only about two years on the average, whereas those patients in whom diabetes was recognized after the age of 40 lived at least four times at long.[2]

Another characteristic of the course of diabetes which is less generally recognized is its tendency to grow more severe the longer it exists, as a rule. Thus, in insulin-treated patients the amount of insulin required to maintain good control tends to increase roughly in proportion to the duration of the disorder. It may show temporary vari-

From Northwestern University Medical School, Chicago, and Evanston Hospital.

1. Woodyatt, R. T.: Diabetes Mellitus, in Cecil, R. L.: Textbook of Medicine, ed. 5, Philadelphia, W. B. Saunders Company, 1941, p. 687.

2. Joslin, E. P.: Treatment of Diabetes Mellitus, ed. 7, Philadelphia, Lea & Febiger, 1940, p. 275.

ations in both directions due to modifying influences, such as painstaking or careless treatment or infection and other complications. But as the diabetes persists, more insulin is usually required, until a level is reached which is characteristic of the individual case, commonly 40 to 60 units daily with diets of moderate value.

In clinical practice the severity of diabetes mellitus may be judged by a variety of gages. Some of the more obvious are as follows: (1) the amount of food tolerated without excessive glycosuria and hyperglycemia (this is of value only in cases of mild diabetes); (2) the rapidity with which glycosuria and hyperglycemia develop and their magnitude under conditions creating them, such as excesses of food, deficiencies in insulin effect and infections; (3) the ease with which ketogenic acidosis occurs and its intensity; (4) the degree of sensitivity to excesses of insulin, and (5) the size of the daily insulin dose required to maintain good control.

From the standpoint of quantitative study it is obvious that the most useful of these gages of severity is the size of the dose of insulin. If subjects with typical diabetes of every grade could be watched for years under unchanged conditions of treatment, much could be learned. But diets and technics of insulin control change; so data obtained in such a manner would not be comparable.

Data of almost equal value may be obtained in another manner. Instead of comparing the amount of insulin needed by the same patients at different times, the insulin required by different patients may be compared at the same time. Such data, although lacking the advantage of measuring the progress of a given set of patients, do possess the advantage of being strictly comparable as to details of diet and insulin management, which seems equally important, if not more so.

Hence, a group of patients treated under uniform conditions was analyzed to determine the relation between the need for insulin and the duration of the existing diabetes at various ages. Interpretations of such data must be based on the assumption that in any group of patients managed by diets of uniform value the need for insulin gives a fair estimate of the severity of the diabetes and that an increased need indicates progression of the diabetes. It is clearly recognized that this assumption may be misleading in any individual subject. Variability in insulin sensitivity,[3] complications, exercise,[4] consistency of

3. Radoslav, C. S.: Ueber die Wirkung des Insulins auf den Blutzucker beim Menschen, Wien. Arch. f. inn. Med. **8**:395-412 (July) 1924. Himsworth, H. P.: Diabetes Mellitus: Its Differentiation into Insulin-Sensitive and Insulin-Insensitive Types, Lancet **1**:127-130 (Jan. 18) 1936. MacBryde, C. M.: Response to Insulin as an Index to the Dietary Management of Diabetes, J. Clin. Investigation **15**:577-589 (Sept.) 1936. Klatskin, G.: The Response of Diabetics to a Standard Test

(Footnotes continued on next page)

treatment, emotion,[5]—these and other factors affect the need for insulin profoundly in individual subjects. Yet when groups of subjects are employed such irregularities are minimized by averaging, and errors from this source are probably fairly constant in all groups.

On the assumption that such data provide an approximate view of the course of diabetes mellitus it is possible to confirm and augment the idea that diabetes progresses more rapidly the earlier in life it begins and that up to a certain limit it becomes more severe the longer it exists.

Of greater interest, however, such data support the theory of the inherent nature of diabetes. They also provide a rough concept of the stage of "potential diabetes" preceding the recognizable onset of the disease, as well as the level of normal insulinogenic function which exists even before the potential stage is reached. Finally, these data suggest the possibility that diabetes may be a self-limited or curable disease after it exists for a long time.

METHOD

Each patient in a group of 166 with proved diabetes was judged carefully from three standpoints: first, the age at which the diabetes was recognized (age at onset); second, the length of time it was known to have existed up to the time of study (duration), and third, the daily dose of insulin necessary for satisfactory control of the diabetes (insulin dose).

These patients when studied ranged from 6 to 82 years of age. Their diabetes had begun at 2 years of age in the youngest and 77 years in the oldest. The age distribution was approximately uniform; about one quarter were less than 20 years old and one third more than 50 years old at the onset of diabetes. About two thirds were females.

In no case was any acute complication present at the time of study. Some chronic complications existed, particularly in the older patients; these subjects were not excluded, and the significance of their complications will be discussed later.

Age at Onset and Duration of Diabetes.—The age at onset was estimated in each case from a careful history of the date of onset of unmistakable symptoms or, if a patient was asymptomatic, of the first discovery of glycosuria. In practically all cases this date could be ascertained quite definitely with no probable error greater than a few months in the majority. In each case the duration of the diabetes up to the time of study was then taken for computation of group averages.

Dose of Insulin, ibid. **17**:745-750 (Nov.) 1938. Burgert, P.; Scott, R., and Nadler, W. H.: A Comparison of Tests for Insulin Sensitivity, Proc. Central Soc. Clin. Research, 1938, p. 23.

4. Lawrence, R. D.: The Effect of Exercise on Insulin Action in Diabetes, Brit. M. J. **1**:648-650 (April 10) 1926. Gerl, A., and Hofmann, A.: Muskelarbeit und Insulinbedarf beim Diabetes, Klin. Wchnschr. **7**:59-63 (Jan. 8) 1928. Richardson, R.: Factors Determining the Effect of Exercise on Blood Sugar in the Diabetic, J. Clin. Investigation **13**:699 (July) 1934. Marble, A., and Smith, R. M.: Exercise in Diabetes Mellitus, Arch. Int. Med. **58**:577-588 (Oct.) 1936.

5. Woodyatt, R. T.: Psychic and Emotional Factors in General Diagnosis and Treatment, J. A. M. A. **89**:1013-1014 (Sept. 24) 1927.

Groups of subjects for averages were formed as follows: All patients were classified in seven groups of 12 to 39 each according to the decade of life in which diabetes began. Those in each decade were then further subdivided into six smaller groups of 1 to 8 patients (usually 4 or 5) according to the length of time the diabetes had existed. For example, there were 33 patients whose age at onset was 41 to 50 years, inclusive. These 33 patients were further subdivided into six subgroups, in which the average duration of diabetes was approximately one, two, five, eight, thirteen and twenty-three years, respectively, at the time of study.

In each of the subgroups the average daily dose of insulin required for good control (as defined in the following section) was taken as the insulin dose for the group.

Insulin Dose.—In all cases the diabetes was regulated according to uniform criteria for satisfactory control. These criteria were as follows:

1. The use of diets capable of maintaining or obtaining ideal weight at normal activity and sufficient for normal growth in children.

2. Carbohydrate to fat ratio in grams of about 1:1. Accordingly, the average adult diet contained about 2 Gm. of carbohydrate per kilogram of body weight, 1 Gm. of protein and 2 Gm. of fat, providing about 30 calories per kilogram. In diets for obese subjects the fat was arbitrarily reduced to permit weight reduction, the carbohydrate value remaining comparable to that of the diets for other patients.

3. Freedom from glycosuria and excessive hyperglycemia except in a group of patients susceptible to hypoglycemic symptoms. In those patients, as much insulin was used as possible without hypoglycemia and as little glycosuria as possible was permitted.

4. Freedom from frequent hypoglycemia.

5. Insulin effects predominantly from protamine zinc insulin in a single dose daily, often alone, but frequently supplemented by a small daily (rarely twice daily) dose of ordinary insulin.

These criteria conform to those in general use today in practice, their chief distinguishing characteristics represented by the use of diets of only moderate carbohydrate content, perhaps a little less liberal than average in this country but generous enough not to approach a ketogenic level. Their ketogenic ratio (FA/G, Woodyatt[6]) was about 0.8.

Preliminary adjustment was accomplished in the Evanston Hospital under quantitative conditions. Further minor adjustments were then made until the weight behavior became satisfactory and the amount of insulin required daily for good control became relatively stable. This daily insulin dose was then averaged with those of other patients with diabetes beginning in the same decade of life and existing for approximately the same length of time, in small groups of subjects as just described.

Some 20 per cent of the patients did not require insulin for control and were included in the group averages with insulin doses of zero. It would obviously be unfair for the purposes of this paper to omit them.

RESULTS

The table shows the values obtained in this manner in each of about forty small groups of comparable subjects. The table also shows the number of patients responsible for the average values in each group.

6. Woodyatt, R. T.: Objects and Method of Diet Adjustment in Diabetes, Arch. Int. Med. **28**:125-141 (Aug.) 1921.

The chart shows graphically the insulin needed after various periods of diabetes in each decade. Each point on a curve represents the average for one of the smaller groups of comparable patients, with

Daily Insulin Dose Required for Control of Diabetes in Various Age Groups at Various Stages of Its Course in One Hundred and Sixty-Six Subjects

Age at Onset, Yr.			Number of Years Since Onset of Diabetes *						No. of Subjects	Average Annual Insulin Increment, Units †
Range	Average		0-1	1-3	3-5	5-10	10-15	15-30		
First Decade										
2-10	6	Insulin dose, units..	27	42	45	56	63	52		7.2
		Years since onset....	1—	2+	4	8—	13—	17		
		No. of subjects.....	3	4	2	4	7	1	21	
Second Decade										
11-20	14	Insulin dose, units..	20	44	52	74	56	40		5.1
		Years since onset....	1—	2+	4	8	13	22		
		No. of subjects.....	4	4	1	3	3	3	18	
Third Decade										
21-30	26	Insulin dose, units..	12	37	30	49	60	27		3.8
		Years since onset....	1	2+	4+	10	14	18		
		No. of subjects.....	1	4	4	1	2	5	17	
Fourth Decade										
31-40	37	Insulin dose, units..	15	12	50	29	40	16		3.2
		Years since onset....	1—	2	4	7+	14	19		
		No. of subjects.....	2	1	1	6	1	1	12	
Fifth Decade										
41-50	46	Insulin dose, units..	17	6	15	33	15	20		1.9
		Years since onset....	1—	2	5	8+	13	23		
		No. of subjects.....	5	4	2	16	4	2	33	
Sixth Decade										
51-60	55	Insulin dose, units..	5	18	9	12	31	26		2.0
		Years since onset....	1—	3—	4+	7	12+	20		
		No. of subjects.....	5	8	5	8	8	5	39	
Seventh and Eighth Decades										
61-77	66	Insulin dose, units..	24	12	18	21	23	..		4.2
		Years since onset....	1—	3—	4+	8—	13			
		No. of subjects.....	5	5	4	5	7	0	26	

* In each of the small groups the insulin dose and the number of years since onset represent averages for those subjects in the group.

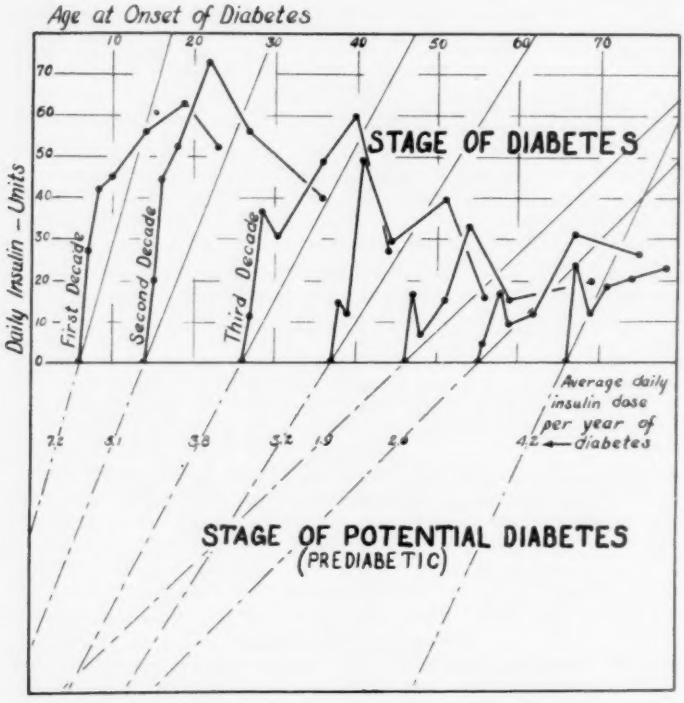
† The annual insulin increment in each decade was obtained by calculating the average rate of increase in required insulin in units per year of diabetes.

the insulin dose in units per day as the abscissa and the years of existing diabetes as the ordinate. The mean curve for each decade was obtained by calculating the rate of increasing need for insulin, or average annual increment, in units per year of diabetes. These increment curves were projected into the "prediabetic," or "potential diabetic," stage, on the theory that the rate of progression of diabetes is probably about the same before as after it makes its appearance clinically.

INTERPRETATION

Four phenomena are apparent from a study of the actual insulin curves.

1. The earlier in life the diabetes appeared the more rapidly the need for insulin increased. This is true in all decades except the last, in which it is probable that the frequency of chronic complications increased the insulin required.



Relation between the age at which diabetes begins and the subsequent daily need for insulin.

2. Except for minor irregularities (discussed later) the longer the diabetes existed the greater was the need for insulin at all ages.

3. In all but the first two decades the initial rapid increase in insulin was followed by a temporary decrease, which occurred as early as the second or the third year and sometimes persisted through the fifth year of the disease. It tended to appear later and persist longer the greater the age at onset. Hence, it was probably missed in the first two decades because the data were not analyzed for periods shorter than the first year.

Individual examples of this phenomenon are well known, and it is usually anticipated in practice. Often there is complete freedom from the need for insulin for a short time following discovery and initial control of the diabetes. The improvement is probably due to a temporary gain in natural insulinogenic function due to accurate control. It does not appear to modify the ultimate course of the diabetes.

4. In all decades but the last there was an unmistakable tendency for required insulin to fall off somewhat after long persistence of the disease. Thus, after nine to fourteen years of diabetes (about ten on the average) in every decade up to 60 less insulin was required than previously. In a few individual subjects some thirty years of diabetes failed to alter this tendency toward improvement.

Two striking examples of this phenomenon are included in the group of 166 subjects. In 1 patient typical juvenile diabetes appeared at the age of 15. For fifteen years it followed the usual pattern of dependence on insulin in a dose as great as 50 units daily, difficulty of keeping under control, occasional severe acidosis or hypoglycemia and frequent glycosuria. Then at the age of 30 the insulin requirement began to decline. Five years later for about a year prior to death from chronic nephritis (intercapillary glomerulosclerosis[7]) insignificant glycosuria and hyperglycemia appeared when insulin was stopped, and doses as small as 10 units of protamine insulin caused hypoglycemia.

In another patient diabetes began at the age of 47. After about ten years of control by diet insulin was used continuously for about fifteen years in doses as large as 60 units daily. Heavy glycosuria occurred at intervals; there was no acidosis, and good health was maintained. Now, twenty-six years after the onset of the diabetes, this patient is exceptionally well at the age of 73, eats a generous diet only moderately restricted and for nearly a year has been free of sugar without any insulin whatsoever.

Cases in which diabetes disappears are described in the literature.[8] Every clinician who treats much diabetes observes an occasional instance.[1] It is not uncommon in the diabetes accompanying acromegaly.[9] However, a consistent tendency for ordinary diabetes mellitus to improve in time has not been noted previously.

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7. Kimmelstiel, P., and Wilson, C.: Intercapillary Lesions in the Glomeruli of the Kidney, Am. J. Path. **12**:83-98 (Jan.) 1936. Newburger, R. A., and Peters, J. P.: Intercapillary Glomerulosclerosis: A Syndrome of Diabetes, Hypertension and Albuminuria, Arch. Int. Med. **64**:1252-1264 (Dec.) 1939. Porter, W. B., and Walker, H.: The Clinical Syndrome Associated with Intercapillary Glomerulosclerosis, J. A. M. A. **116**:459-464 (Feb. 8) 1941.

8. Naunyn, B.: Der Diabetes mellitus, ed. 2, Vienna, A. Hölder, 1906.

9. Colwell, A. R.: The Relation of the Hypophysis to Diabetes Mellitus, Medicine **6**:1-39 (Feb.) 1927.

The longer life span of a diabetic patient due to insulin makes it possible to observe the late course of the disease, especially in the case of patients who are young when diabetes begins. The tendency for required insulin to decrease eventually suggests the possibility of ultimate spontaneous cure of diabetes, assuming that patients can live long enough for it to occur. During the next ten or twenty years sufficient experience will have been gained to determine whether this course is usual or exceptional. The data here reported suggest that it may be the usual course after ten years or more.

The mean slopes are constructed by calculating the rate at which required insulin increases annually in each decade, i. e., the average insulin increment per year of diabetes. The minor decreases observed early and late are included in the averages as minus values, or decrements. Thus, on the average, the insulin required drops steadily from 7 units per year in patients with diabetes having its onset in the first decade to 2 units per year in patients with diabetes beginning in the fifth and the sixth decade.

If these average insulin rates are taken as approximate gages of diabetic progress in all decades, it is apparent from extension of their slopes that the origin and the magnitude of the prediabetic stage may be estimated. If one accepts the view that diabetes progresses at about these rates, both before and after it is recognized, two other important inferences involving the preclinical stage of diabetes are possible.

1. Its course begins about the time of birth, no matter how late in life it is recognized. In each decade except the last (in which chronic complications apparently alter the data), the average insulin curves showing the probable rate of progress tend to converge when extended backward into the "prediabetic stage." The point of convergence approximates the time of birth, indicating that diabetes of a predetermined type is inherited, begins its course at birth and progresses through an unrecognized phase at a rate which continues, with minor variations, after its discovery. This concept agrees with that which is generally accepted on the basis of other data.[10]

2. Its course is approximately half run by the time it is recognized clinically. The slopes which represent the average increments of insulin required annually tend to converge at an insulin level distant from that existing when the diabetes appears. If one grants that these average insulin curves represent the approximate course of the diabetes and that the course is about the same before as after discovery, the prediabetic stage appears to be at least as great in magnitude as the observed diabetic stage which follows. In other words, at least

10. White, P.: Diabetes in Children, Bull. New York Acad. Med. **10**:347-357 (June) 1934; Recent Progress in Severe Diabetes, Canad. M. A. J. **35**:153-161 (Aug.) 1936. White, P., and Pincus, G., in Joslin.[2]

as much insulinogenic function is lost by a diabetic person before as after diabetes makes its clinical appearance.

This concept agrees with other data which indicate the magnitude of the normal capacity for utilizing sugar. Woodyatt, Sansum, Wilder and Felsher [11] found that nearly 1 Gm. of dextrose per kilogram per hour could be injected continuously into the veins of normal human beings and animals without glycosuria. In an average person weighing 70 Kg. during fourteen or fifteen hours daily of food absorption this would indicate a normal tolerance for dextrose of about 800 Gm. daily, which is about twice the amount of sugar tolerated by patients with the mildest known diabetes without glycosuria.

SUMMARY

If one employs the amount of insulin required daily for uniform control as a gage of the severity of diabetes mellitus in groups of patients of different ages and at different stages of the disease, the following interpretations appear to be justified:

1. Diabetes is inherent and begins at birth.
2. Before it is recognized in clinical practice it progresses through a stage the magnitude of which is fully as great as that of the known diabetes which follows recognition.
3. The rate of its progress is indicated by the age at which it is recognized. The earlier it appears, the more rapidly it progresses. It is probably more nearly correct to say the more rapidly it progresses through its unrecognized stage the earlier in life it appears.
4. During the first few years after its recognition it tends to improve temporarily, probably as a result of treatment. This improvement does not affect its subsequent course.
5. After some ten years of known existence there are indications that it may show progressive and permanent improvement.
6. These rules frequently appear to be violated in aged persons with diabetes, probably because of chronic complications.

636 Church Street.

11. Woodyatt, R. T.; Sansum, W. D., and Wilder, R. M.: Prolonged and Accurately Timed Intravenous Injections of Sugar, J. A. M. A. **65**:2067-2070 (Dec. 11) 1915. Sansum, W. D., and Woodyatt, R. T.: Studies on the Theory of Diabetes: VIII. Timed Intravenous Injections of Glucose at Lower Rates, J. Biol. Chem. **30**:155-173 (May) 1917. Felsher, H. V., and Woodyatt, R. T.: Studies on the Theory of Diabetes: IX. Sugar Excretion Curves in Dogs Under Intravenous Injection of Glucose at Lower Rates, ibid. **60**:737-747 (July) 1924.

CINCHOPHEN GASTRIC ULCERS IN CHICKS

GARNETT CHENEY, M.D.
SAN FRANCISCO

The existence of a dietary factor, an absence of which will cause superficial gastric ulcers in chicks, is well recognized by persons interested in the nutrition of poultry.[1] Members of the medical profession at large hardly seem aware of this factor and of the significant fact that definite gastric lesions may be produced experimentally, at least in chicks, by dietary means alone. Of perhaps even greater significance is the recent demonstration that the same type of erosive lesion may be produced by feeding cinchophen, which will cause not only superficial ulcers but the severer types of gastric ulceration encountered in man, including deep penetration and perforation.[2] These cinchophen gastric ulcers differ only in degree from ulcers produced by a deficient diet alone, and they may also be prevented or modified by a dietary factor.

As this important relation exists between these two apparently etiologically different types of experimentally produced gastric ulceration, the present knowledge of the deficiency type has been reviewed and supplemented and in addition further studies are reported concerning the development and the alleviation of cinchophen gastric ulcers themselves.

METHOD

White leghorn baby chicks were used for all the experiments.[3] These chicks were hatched in Petaluma and were received in the laboratory the day of hatching or the subsequent day. They were given a starter mash diet for a few days before being transferred to the experimental diets. They were raised indoors in brooders with screen floors.

From the Department of Medicine, Stanford University School of Medicine.

This investigation was aided by a grant from Eli Lilly and Company, Indianapolis.

1. (*a*) Dam, H.: Antihaemorrhagic Vitamin of Chick, Biochem. J. **29**:1273, 1935. (*b*) Dam, H., and Schonheyder, F.: Occurrence and Chemical Nature of Vitamin K, ibid. **30**:897, 1936. (*c*) Almquist, H. J., and Stokstad, E. L. R.: Dietary Haemorrhagic Disease in Chicks, Nature, London **136**:31, 1935; (*d*) Gizzard Factor of Chick, J. Nutrition **13**:339, 1937. (*e*) Almquist, H. J.: Source and Nature of Gizzard Factor, ibid. **14**:241, 1937. (*f*) Esselen, W. B.: Nutritional Gizzard Lesions in Chicks, Poultry Sc. **18**:201, 1939.

2. Cheney, G.: Effect of Diet and Cinchophen on Production of Experimental Gastric Ulcers in Chicks, Proc. Soc. Exper. Biol. & Med. **45**:190, 1940.

3. The Poehlmann Hatchery, Petaluma, Calif., supplied all the birds used.

TABLE 1.—*Effect of Dietary Supplements on Cinchophen Peptic Ulcers in Chicks*

Series No.	Diet	Supplement	Cinchophen, per Cent	No. of Chicks	Age at Autopsy, Days	Average Weight at Autopsy, Gm.	Grade of Ulceration	Interpretation
S-5-2	Basal diet, see text	None	None	5	20	178.8	1.3	Control
S-5-3		None	0.5	8	21	151.6	2.1	Control fed cinchophen
S-5-5		5% dried leaves of cereal grasses	0.5	8	22	175.0	1.45	Protective
S-5-7		10% dried leaves of cereal grasses	0.5	8	22	171.6	1.5	Protective
S-5-4		None	1.0	8	21	120.0	3.63	Control fed cinchophen
S-5-8		5% dried leaves of cereal grasses	1.0	10	22	101.8	2.4	Protective
S-5-10		10% dried leaves of cereal grasses	1.0	10	21	134.2	2.3	Protective
S-6-1A	Basal diet plus 10 per cent alfalfa	None	None	11	22	179.7	1.0	Control
S-6-1		None	1.0	12	20	141.7	2.67	Control fed cinchophen
S-6-5		20% spinach, wet	1.0	8	20	101.1	3.25	No protection
S-6-6		Milk ad lib.	1.0	8	19	138.0	1.13	Protective
S-6-7		2% of a combination of sodium glycocholate and sodium taurocholate	1.0	8	19	112.5	2.5	No protection
S-6-8		5% AlOHs	1.0	8	20	104.8	3.37	No protection
S-6-3		Chick liver, 2.5 Gm. per bird daily	1.0	6	17	116.0	3.2	No protection
S-6-2A		Chick liver, 2.5 Gm. per bird daily *	1.0	4	17	124.6	2.1	? Protection
S-6-2		Dog liver, 2.5 Gm. per bird daily	1.0	10	18	129.9	1.75	Protective
S-6-4		Dog liver, 10 Gm. per bird daily	1.0	10	18	130.9	2.2	Protective
S-1-3	Vitafood, see text	None	None	10	22	208.0	0.25	Control
S-1-1		None	0.5	8	21	163.4	0.25	Control fed cinchophen
S-1-5		Dog liver, 2.5 Gm. per bird daily	0.5	10	21	184.5	0.15	? Protective
S-1-8		None	1.0	8	21	143.3	0.61	Control fed cinchophen
S-1-6		Dog liver, 2.5 Gm. per bird daily	1.0	10	21	157.9	0.25	Protective
S-1-4		Human liver, 2.5 Gm. per bird daily	1.0	10	21	182.6	0.38	Protective
S-1-9		2% cholic acid	0.5	10	22	157.0	0.33	No protection
S-1-10		2% cholic acid	1.0	10	22	139.3	0.92	No protection
S-1-7		5% mucin	1.0	8	22	133.8	1.28	No protection
S-2-1		Gastron, 3.3 cc. per bird daily	None	8	21	171.5	0.44	Control given gastron
S-2-2		Gastron ad lib.	None	8	10	40.6	?	(See text)
S-1-2		Gastron, 3.3 cc. per bird daily	1.0	10	21	124.4	1.35	No protection
S-3-1	Vitafood heated 6 hours at 80 C.	None	None	10	23	.....	0.2	Control
S-3-4		None	1.0	10	23	161.1	1.95	Control fed cinchophen
S-3-3		Dog liver, 2.5 Gm. per bird daily	1.0	10	23	145.9	1.6	Protective
S-3-5		Dog liver, 2.5 Gm. per bird daily †	1.0	10	23	145.0	2.3	No protection
S-3-7		Dog liver, 2.5 Gm. per bird daily †	1.0	10	23	153.0	2.1	No protection
S-3-6		Evaporated milk	1.0	10	23	153.5	1.05	Protective

* Livers from cinchophen-fed birds.
† Livers from cinchophen-fed dogs.

Each group of chicks ordinarily was made up of 8 to 10 birds. These experimental groups were started in the second week of life when they were first weighed. Autopsy studies were usually carried out between the seventeenth and the twenty-third day. Cinchophen was fed seven to fourteen days preceding autopsy. The weights of the birds were recorded again before and after cinchophen

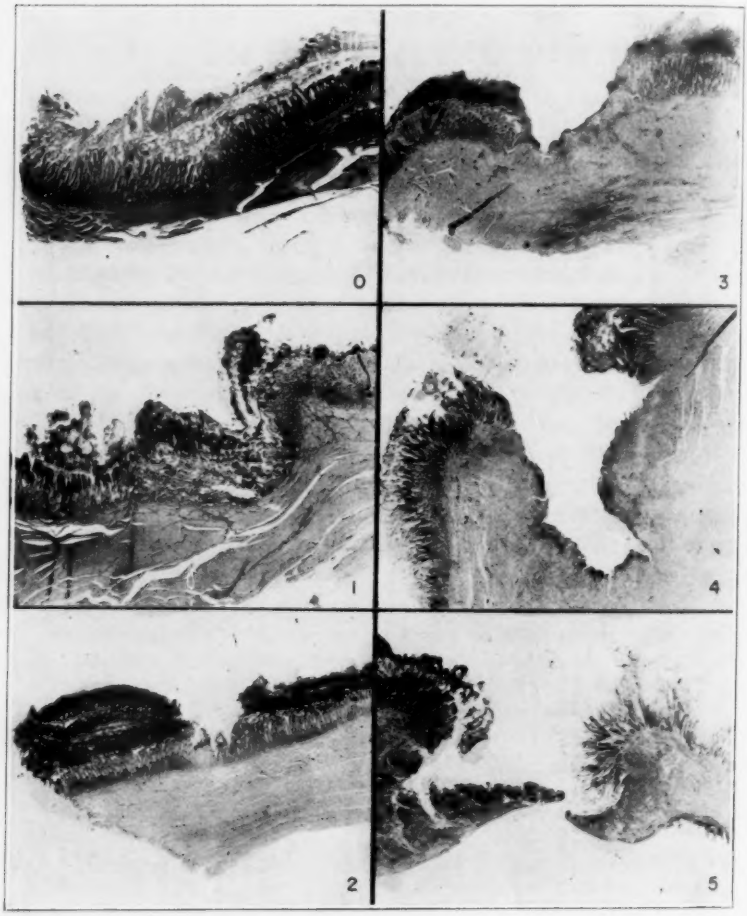

Fig. 1.—Cross sections of chick stomach walls illustrating the method used for scoring different grades of ulceration. *O*, normal wall; *1*, the initial lesion, a mucosal hemorrhage beneath the chitinous lining of the gastric lumen; *2*, superficial erosion with loss of the chitinous layer and flattening of the mucosa; *3*, a peptic ulcer with destruction of the mucosa and with a flat base; *4*, a penetrating ulcer with invasion of the muscle layers, and *5*, a perforating ulcer with peritonitis.

feeding. The special diets were started the third to the fifth day of life, and additional substances to be tested for their protective value against ulceration were added to the diet for a five day period before cinchophen was administered. These substances when dry were thoroughly mixed with the diets; otherwise they were offered separately. A control group of birds was run with each type of diet for each series.

The basal diet previously described was used again.[4] It consists of ether-extracted or gasoline-extracted fish meal 17.5 per cent, brewers' yeast 7.5 per cent, sodium chloride 1 per cent, cod liver oil 1 per cent and rice flour 73 per cent. This diet has repeatedly been shown to be deficient in the anti-gizzard-erosion factor and is also deficient in vitamin K. The diet designated in figure 2 as *2 A* and in table 1 as *B. D. A.* is the same diet plus 10 per cent alfalfa to add bulk. This diet is also deficient, but the incidence of erosions is lower. A commercially prepared mash known as vitafood marketed by the Poultry Producers of California offers

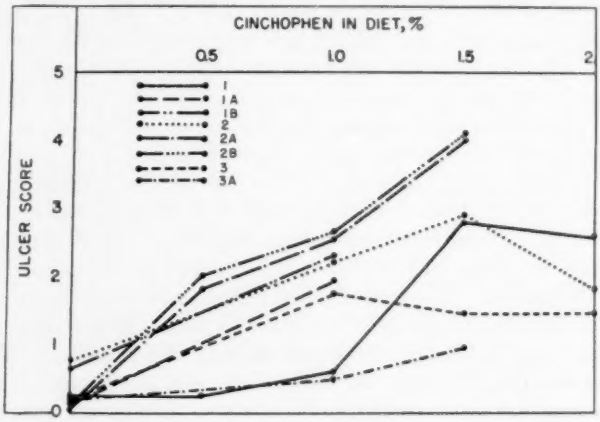

Fig. 2.—Relation of the type of diet and the percentage of cinchophen fed to the grade of gastric ulceration in chicks. *1*, a protective diet; *1 A*, the same diet heated six hours at 80 C.; *1 B*, the same diet heated twenty-four hours at 80 C.; *2*, a deficient nonresidual diet; *2 A*, the same diet plus 10 per cent alfalfa; *2 B*, the same diet plus 25 per cent alfalfa; *3*, a high carbohydrate protective diet, and *3 A*, a high carbohydrate nonresidual diet.

a well balanced diet which has proved protective against gastric ulcers. It consists of protein 18.5 per cent, fat 3.7 per cent, carbohydrate 66.5 per cent, ash 5.8 per cent, fiber 3.8 per cent and minerals (calcium, phosphorus and manganese) 2.1 per cent. It contains 5 per cent dehydrated alfalfa and 0.25 per cent sardine oil fortified with vitamin A. This diet has served satisfactorily as a normal control type of feed.

All birds were autopsied at the end of the series, on the same day if possible. The condition of each gizzard was carefully noted, and the degree of ulceration was observed in the fresh specimen and scored as previously described.[3] The grades of ulceration are shown in figure 1. Grade 1 represents the earliest

4. Cheney, G.: Gastric Acidity in Chicks with Experimental Gastric Ulcers, Am. J. Digest. Dis. **2**:104, 1938.

demonstrable lesion, a mucosal hemorrhage without rupture of the chitinous lining of the gizzard. In lesions of grade 2, rupture has taken place, part of the mucosa is thinned out or destroyed, the evidence of bleeding may disappear and a typical superficial gastric ulcer, or area of gizzard erosion, is present. In lesions of grade 3, the mucosa has largely disappeared and the ulcer has a flat base with punched-out appearance and often with thickened indurated margins. Lesions of grade 4 represent definite penetration into the underlying muscle layers, and those of grade 5, perforation with involvement of the peritoneum. If the exact grading is in doubt, the lesion is scored half way between two grades. For example, if there is a question whether the muscle layer is or is not invaded (grade 4 or grade 3), the lesion is scored as 3.5. At first microscopic sections were made to determine the exact depth of an ulcer, but with experience gross observation of a cross section of the lesion has proved reasonably accurate.

PRODUCTION OF LESIONS

Cinchophen was fed in concentrations of 0.5, 1, 1.5 and 2 per cent thoroughly mixed with the diet. It was soon noted that the 2 per cent level was often so toxic that few birds survived the experiment. Toxic symptoms consisted of weakness, loss of coordination, loss of appetite, marked prostration and occasionally death within twenty-four or forty-eight hours. Ordinarily, the 1 per cent level produced fairly satisfactory gastric lesions without too great toxicity and without causing death of the birds. All the birds fed this amount of cinchophen failed to gain weight as well as the controlled groups, however. The relation of the percentage of cinchophen fed to the production of ulceration is well shown in figure 2. The ulceration becomes progressively more severe as a rule up to the 1.5 per cent level but may be less severe after that in birds surviving the experiment because so little feed is taken. Although it varies with the type of diet fed, the general trend is constant. One half of 1 per cent cinchophen usually produces lesions, but few are more severe than grade 2.

The production of lesions by feeding cinchophen will vary greatly with the type of diet given because of the varying amounts of protective substance contained in the diets, because of the amount of roughage and possibly also because of the carbohydrate content. Figure 2 depicts the varying effects of the diet on the grade of ulceration. An adequate protective diet shows an almost complete absence of lesions in the control experiments and no marked increase until more than 1 per cent of cinchophen is fed. In contrast to this, chicks on a deficient diet show some lesions in the control group and pronounced lesions at the 0.5 per cent level. In chicks on the high carbohydrate protective and non-residual diets only mild ulceration occurred, and in one series (fig. 2 *3 A*) the degree of ulceration in birds fed 1 per cent cinchophen was not as great as that in the control groups on a deficient diet without cinchophen.

Figure 2 also shows the effect of heat on the protective diet. When this diet is heated at 80 C. for six hours, a marked deficiency is manifest when cinchophen is fed, compared to the lesions produced by the same diet without heating. When this diet is heated at 80 C. for twenty-four hours, the deficiency is slightly more pronounced.

When the diet is finely divided, it is evident that cinchophen may be less well retained and consequently toxic effects may be less severe. On the contrary, a bulky diet is retained longer and cinchophen intoxication and gastric ulceration become more marked. This is shown in figure 2 by comparing the degree of ulceration produced by a deficient nonresidual diet and that produced by the same diet to which alfalfa has been added. This is most obvious at the 1.5 per cent level. At this level the grade of ulceration is 2.9 without alfalfa but is 4.0 when 10 per cent alfalfa is added and is 4.1 when 25 per cent is added, despite the protective value of alfalfa meal when it is fed liberally.

The importance of the diet in producing lesions is best understood by noting the marked differences of effect of the same amount of cinchophen when the different feeds contain various amounts of the protective substance. At the 0.5 per cent level the degree of ulceration varies between 0.25 and 2. At the 1 per cent level it varies between 0.5 and 2.65. At the 1.5 per cent level it varies between 0.95 and 4.1. In the 3 experiments at the 2 per cent level, it varies between 1.45 and 2.6. However, as already noted, the degree of ulceration is fairly consistent for a given diet at a given level of cinchophen. This was noted repeatedly in feeding 1 per cent cinchophen to different series of chicks when each group fed was on the same diet.

PATHOLOGIC OBSERVATIONS

Grossly the gastric lesions vary greatly in form, as indicated by the method of grading the severity of the ulceration, shown in figure 1. The earliest noticeable change is a darkly stained area visible beneath the chitinous layer, which in cross section represents a hemorrhage into the gastric mucosa. This area of bleeding may be only a millimeter in diameter or may be diffuse and extensive. It may be localized to several different areas. It is best seen in the lesions due to dietary deficiency alone and particularly in birds which are also deficient in vitamin K. Actual erosions with loss of the chitinous layer over an area of thinned-out mucosa are the common lesions encountered and may vary considerably in size and number. They may be classified as superficial ulcers, although no real tissue necrosis has taken place. As the lesion becomes deeper, it may assume various forms, appearing funnel shaped, triangular, punched out or, not infrequently, flat based with rolled and

indurated edges, as shown in figure 3. As penetration through the mucosa into the muscle layers occurs, the ulcer appears grossly identical with the peptic lesions so well described in human beings. There is no evidence of gastritis associated with these ulcers.

An ulcer existing a number of days or perhaps a week may be almost pinpoint in size or may appear as an extensive area of roughening, presenting a "chewed-up appearance" of the inner lining. Large ulcers

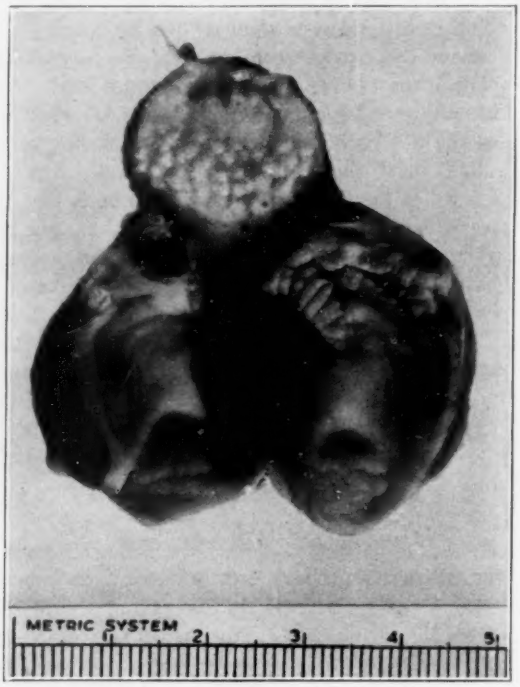

Fig. 3.—A typical large ulcer of grade 3 with a flat base and indurated margins. It is in the muscular part of the bird's stomach (gizzard) just below the fundus, a common site.

1 cm. in diameter occasionally occur, but the average erosion is somewhat irregular in outline and commonly covers a surface a few millimeters in diameter. Deep penetrating ulcers are more likely to be small in appearance than large.

Usually more than one lesion is evident in a stomach which is affected, but different grades of ulceration may occur in the same organ. A group

of 69 chicks was studied from the point of view of incidence of single and multiple lesions and the severity of ulceration occurring. All of these chicks were fed on the basal diet containing 10 per cent alfalfa to which 0.5 or 1 per cent cinchophen had been added. The average ulcer score for the whole group was 2.78. Only three stomachs were free from lesions. Of the 66 stomachs in which lesions were found, there were only single ulcers in 18, or 27.3 per cent, while the rest showed two or more ulcers. Fifteen showed two; 10 showed three; 7 showed four, and in the remaining 16 there were more than four lesions per stomach. In the 53 stomachs in which the number of lesions was counted there were one hundred and six ulcers. If one graded the individual stomachs according to the severest lesion found, there were seven lesions of grade 1, thirty of grade 2, fifteen of grade 3, ten of grade 4, and four of grade 5. It is noteworthy that all four of the perforating ulcers and four of the penetrating ones were single lesions. Occasionally, a single stomach would show two or three grades of lesion, and rarely a lesion of grade 1 and one of grade 4 or 5 would be present in the same stomach wall.

It is a striking feature that the vast majority of lesions are limited to the submarginal area, that is, just below the juncture of the chitinous lining of the gizzard with the smooth mucous membrane–lined intermediate zone which connects the upper glandular fundus, or proventriculus, with the lower, muscular part of the stomach. This area is where the acid, pepsin-containing juice of the fundus first strikes the lining of the gizzard. Not infrequently superficial lesions occur in the distal pouch of the gizzard, where acid gastric juice enters freely. However, no penetrating or perforating ulcers have been noted in this distal region.

As previously pointed out, ulcers do not occur in the fundus of the stomach or in the intermediate zone. They appear only in the muscular portion of the stomach, which does not secrete acid or pepsin. No lesions have ever been noted at the duodenal orifice, but in the chick the duodenum leaves the gizzard at a right angle, some distance below the submarginal area, and consequently is not bathed by acid gastric juice.

Occasionally, ulcers not only penetrate the muscular layer but perforate through the serous lining into the peritoneal cavity. This has never been observed in lesions due to dietary deficiency alone. The penetration most commonly occurs just below the intermediate zone and not infrequently into the liver bed. Penetrating ulcers are sometimes small and may be difficult to visualize from the side of the gastric lumen without making a cross section of the stomach wall. Perforation has been noted as early as the fifth day of cinchophen feed-

ing, and, as already pointed out, the perforating lesion is not infrequently the only one occurring. When perforation occurs, a localized abscess with peritonitis may form or diffuse peritonitis may occur with fluid collection and abdominal distention. In 1 sick chick a large gas bubble could readily be observed through the distended abdominal wall indicative of a pneumoperitoneum. At autopsy this bird had a peritoneal cavity distended with gas and fluid and a perforating ulcer approximately 1 mm. in diameter.

Fig. 4.—Multiple stomach ulceration, grade 5, with one perforating lesion.

Histologically, the superficial lesions show changes in the chitinous layer and gastric mucosa which have already been carefully described.[5] I have verified these repeatedly. As the ulcers become deeper, and particularly when they penetrate the muscle layer, the same characteristic histologic changes develop which occur in peptic ulcers in human

5. Lansing, A. I.; Miller, D., and Titus, H. W.: The Formation of Erosions of the Gizzard Lining in the Young Chick, Poultry Sc. **18**:475, 1939. Esselen.[1f]

beings. There are tissue edema and necrosis with vascular engorgement and extensive polymorphonuclear leukocytic infiltration. Also an infiltration with eosinophils is common in the advanced lesions. An increase in fibroblasts occurs below the base of the ulcer. These changes are well depicted in figure 5, which shows a deeply penetrating large gastric

Fig. 5.—A photomicrograph of a penetrating subacute ulcer of grade 4, with an overhanging margin and a necrotic base beneath which is granulation tissue. There is a pronounced infiltration of polymorphonuclear leukocytes and eosinophils.

ulcer from a bird fed cinchophen one month before it was autopsied. The late effects of chronicity and partial healing have not been studied, as the chicks have not as yet been kept under observation sufficiently long to afford a proper opportunity.

DEVELOPMENT AND COURSE OF ULCERATION

The development of gastric ulcers will vary not only with the type of diet fed but with the age and parentage of the bird. When newly hatched chicks are raised on a deficient diet, erosions begin to appear during the second week of life and are most pronounced by the third and the fourth week, when they are usually present in 90 to 100 per cent of the birds. As the birds grow older, evidence of the deficiency becomes progressively less marked.[4] Chicks reared on an adequate diet during the first month and then placed on a deficient diet rarely show pronounced lesions. Occasionally, an embryo chick, a newly hatched chick or an older bird on the usual practical diet may show erosion of the gizzard.[6] Chicks from hens kept on a deficient diet will show lesions earlier in life than chicks from well fed hens.[7]

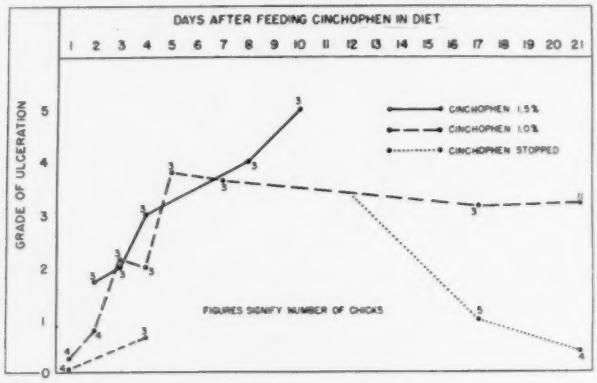
DAYS AFTER FEEDING CINCHOPHEN IN DIET
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
GRADE OF ULCERATION
0 1 2 3 4 5
CINCHOPHEN 1.5%
CINCHOPHEN 1.0%
CINCHOPHEN STOPPED
FIGURES SIGNIFY NUMBER OF CHICKS

Fig. 6.—The development of gastric ulceration in chicks when 1 per cent cinchophen (broken line) and 1.5 per cent cinchopen (continuous line) are added to a basal diet including 10 per cent alfalfa and when 1 per cent cinchophen (chain line) is added to the same basal diet including 25 per cent alfalfa. Rapid improvement (dotted line) occurred after cinchophen feeding was stopped.

When cinchophen is added to the diet during the second week of life, the onset of ulceration will vary not only with the type of diet used but with the amount of cinchophen fed. Repeated observations of chicks on varying diets containing 1 per cent cinchophen reveal no more evidence of gastric ulceration twenty-four hours after cinchophen feeding is started

6. (*a*) Almquist, H. J., and Stokstad, E. L. R.: A Nutritional Deficiency Causing Gizzard Erosions in Chicks, Nature, London **137**:581, 1936. (*b*) Jungherr, E.: Bulletin 202, Connecticut Agricultural Experiment Station, 1935, p. 52.

7. Almquist, H. J.: Personal communications to the author.

than might be attributed to a deficient diet alone, although many of the birds show obvious toxic symptoms. Of the 8 birds autopsied the day after the experiment in figure 6 was started, only 1 showed a lesion, and this was without ulceration (grade 1). Also, only 1 of the 4 birds autopsied after the second day showed a lesion, and this was of the same type. It is evident from these observations that the gastric lesions do not develop as a direct result of toxic action of the cinchophen on the gastric lining but as a late and possibly indirect effect. Feeding cinchophen at the 1.5 per cent level produces ulceration earlier and in a more severe form.

In figure 6 the effects of feeding cinchophen at the 1 and the 1.5 per cent level in different series of birds is compared. The series receiving 1 per cent cinchophen was started at 10 days of age and the series receiving 1.5 per cent at 13 days. Both received the basal diet plus 10 per cent alfalfa. Small groups of birds were autopsied at intervals, as shown on the chart. Of those receiving the larger amount of cinchophen, all showed lesions after the second day, and the degree of ulceration steadily advanced, until after ten days the 3 birds studied all had perforated ulcers (grade 5). The degree of ulceration in the birds receiving 1 per cent cinchophen advanced to an average grade of ulceration of 3.8 in 3 birds after five days, including 1 bird with a perforated ulcer and peritonitis. The degree of ulceration diminished somewhat during the next sixteen days, averaging slightly over 3. On the twelfth day of feeding cinchophen was removed from the diet of 9 of these birds, and five days later 5 birds were autopsied. All showed lesions so slight that they were interpreted as healing. Only 1 showed any definite erosion. The average grade was only 1. The remaining 4 birds were autopsied four days later. Two showed no lesions, and 2 showed only questionable lesions. It is obvious that rapid healing of ulceration occurs when cinchophen is removed from the diet. This corresponds to the improvement already reported in lesions produced by a deficient diet alone when the deficiency is rectified.[8]

Figure 6 also shows that lesions develop more slowly when a protective diet is fed to which 1 per cent cinchophen is added. Seven 11 day old birds were fed on a basal diet to which 25 per cent alfalfa had been added instead of 10 per cent. Autopsies of 4 birds not only failed to show lesions after the first day, but the 3 remaining birds killed after four days did not show gastric ulceration. Two had mucosal hemorrhages. The average grade for the 3 birds was only 0.67.

8. Cheney, G.: Gastro-Enterology in 1936: Selected Topics, Arch. Int. Med. 60:705 (Oct.) 1937.

THE PREVENTIVE SUBSTANCE

The protective substance which has been known as the anti-gizzard-erosion factor was originally thought to be identical with vitamin K. In the earlier experiments with diets deficient in this antihemorrhagic vitamin gizzard erosions were almost constant and were considered one of the cardinal manifestations of the deficiency. The bleeding tendency produced lesions of the gastric lining grossly simulating a hemorrhagic erosive gastritis and occasionally single gastric ulcers with severe and even fatal hemorrhage. However, five years ago Almquist and Stokstad [9] clearly showed that the stomach erosions were not dependent on vitamin K deficiency. In the presence of adequate amounts of all the known vitamins in a vitamin K–deficient diet the erosions still occurred, even when vitamin K was administered in its natural form. I have repeatedly confirmed these observations by adding synthetic forms of vitamin K to vitamin K–deficient diets and noting the same incidence of ulceration as when no vitamin K had been added. This necessitated postulating the presence of an additional substance or factor closely associated with K. Almquist and Stokstad [10] have shown that it is a fat-soluble sterol, but unlike vitamin K it is in the saponifiable fraction.

A variety of substances have been tested for the presence of this factor. The results presented have been derived from the publications of Almquist and Stokstad,[11] from personal communications with Almquist,[7] from articles by Dam and Schonheyder [12] and by Bird and his co-workers [13] and from heretofore unpublished experiments of mine. Alfalfa meal is a known standard source of protection, but its effect is complete only when it is fed at the 20 to 25 per cent level of diet. Different lots of alfalfa vary considerably in potency. Fresh kale and kale extract are highly effective at the 5 per cent level. Hempseed meal is protective at the 10 per cent level. Dried hog liver is protective at the 20 per cent level.

9. Almquist and Stokstad (footnotes 1 *d* and *e* and 6 *a*).

10. Almquist, H. J.: The Effect of Hemp Seed Preparations and of Fineness of Diet on the Chick Gizzard Lining, Poultry Sc. **27**:155, 1938; footnote 1 *e*.

11. Almquist and Stokstad (footnotes 1 *c* and *d*). Almquist.[10]

12. Dam, H.: Hemorrhages in Chicks Reared on Artificial Diets: New Deficiency Disease, Nature, London **133**:909, 1934. Dam, H., and Schonheyder, F.: A Deficiency Disease in Chicks Resembling Scurvy, Biochem. J. **28**:1355, 1934. Footnotes 1 *a* and *b*.

13. Bird, H. R.; Oleson, J. J.; Elvehjem, C. A.; Hart, E. B., and Halpin, J. G.: Relation of Grit to the Development of the Gizzard Lining in Chicks, Poultry Sc. **16**:238, 1937. Bird, H. R.; Kline, O. L.; Elvehjem, C. A.; Hart, E. B., and Halpin, J. G.: The Distribution and Properties of the Anti-Gizzard-Erosion Factor Required by Chicks, J. Nutrition **12**:571, 1936.

and hog liver fat and certain fractions of it are protective when they constitute as little as 3 per cent of the feed. Clarified wheat bran oil is effective when as little as 1.37 per cent is fed in the diet.

A number of substances commonly used in the diet of human beings have been shown to contain this factor. Wheat bran is protective when it comprises 30 per cent of the diet and so is barley bran at the 62 per cent level. Other foods are cooked spinach 20 per cent; canned mixed greens 0.5 per cent dry weight; dried leaves of cereal grasses (cerophyl) 1 per cent; certified raw whole milk, pasteurized whole milk, buttermilk and 20 per cent cream fed in place of water; raw egg yolks when fed in the proportion of ⅕ yolk per chick per day for fourteen days; olive oil 10 per cent; fresh tomatoes ad libitum, and soy bean oil 10 per cent.

The following wide variety of substances has been shown to be completely or relatively impotent under the experimental feeding condition carried out: rice flour and bran; sardine meal; casein; brewers' yeast; ground barley, yellow corn, oats and rye; soy bean meal; peanut meal; sesame meal; linseed meal; black and white sunflower seed; orange meal; cod liver oil; wheat germ oil; copra, soya bean, rapeseed and linseed oil and oil of orange; dried skim milk; dried whole milk; dried chicken livers; hard boiled eggs (twenty minutes), yolk and white; fresh lemon juice; fresh yellow carrots; fresh lettuce and fresh spinach; fresh green peas; artichokes; papaya; garlic; canned tomato juice; lard; avocados; dilute, concentrated and dry liver extracts given by mouth and sterile liver extracts administered by injection; dried calf brain; dried ox muscle; dried ox tongue, and dried calf thymus.

Other substances tried out for protective potency and found wanting are cholesterol, phytosterol, carotene, yeast sterols, alpha tocopherol, phytol, glucuronic acid, acacia, agar, choline, creatine, phytic acid, aloin, linoleic acid, copper sulfate, sodium acid phosphate, glycerine, cotton pulp and sand.

The use of stomach extracts has been most enlightening. Almquist fed dried normal chicken gizzard linings at the 5 per cent level, which gave excellent protection, while diseased linings from chickens on a deficient diet were not effective. I found dried whole hog stomach extract and normal human gastric mucosa dried at 37 C. protective both at the 1 per cent and at the 5 per cent level. Only 1 of 8 birds fed on a deficient diet plus a supplement of 5 per cent hog stomach mucosa had a gastric lesion, giving an ulcer score of 0.25; while lesions developed in 6 of 9 birds receiving a 1 per cent supplement, giving a score of 0.89. Lesions developed in all of 11 birds of the control series without hog mucosa. The ulcer score was 1.7 per cent. A commercial preparation of hog stomach extract (ventriculin) was fed as a 5 per cent supplement to 8 birds, and lesions developed in 4, giving an ulcer score of 0.75. As

the control score for this experiment was 1.13, the margin of protection was not so pronounced as with the first series. Almquist and Mecchi [14] reported negative results with dried stomach lining but did not state the source of their material, the method of drying or the amounts fed.

Similarly, 7 birds were fed 5 per cent normal human gastric mucosa as a supplement, in none of which lesions developed; while lesions occurred in 4 of 6 birds fed a 1 per cent supplement, giving a score of 0.83. The results for the control group were the same as those obtained with hog mucosa extract.

A commercial extract of pepsin fed at the 5 per cent level failed to produce any effect on the incidence of gastric lesions when fed alone or with 0.1 per cent of dilute hydrochloric acid administered in the drinking water. Higher concentrations of acid tended to cause gastric mucosal hemorrhages, general intoxication and frequently an early death.

A number of therapeutic agents commonly employed in treating peptic ulcers in human beings were administered to chicks on a diet deficient in the anti-gizzard-erosion factor. The only one which may have been successful was powdered aluminum hydroxide fed at the 5 per cent level. The grade of erosion in 5 birds was low, 0.3, but the control group in this series showed an ulcer sore of only 0.75. Soda bicarbonate 1 per cent, magnesium trisilicate 5 per cent, gastric mucin 10 per cent, gelatin 5 per cent and daily injections of 0.1 cc. of histidine for twenty-one days failed to protect the birds from lesions.

The protective substance is readily destroyed by heat. This was first demonstrated by Almquist and Stokstad in 1937.[14] It was shown that preparations of dried kale heated at more than 100 C. for twenty-four hours lost completely their power to prevent gizzard erosions. Also soy bean oil and wheat bran, which afford fair protection at the 10 per cent level, failed to protect when heated at 120 C. for twenty-four hours. In 1938 I found that although fresh egg yolks offered good protection against gastric erosion due to dietary deficiency, three-minute boiled yolks offered less protection and yolks boiled for twenty minutes offered poor protection. The relative ulcer scores for a group on each of these three experimental foods were 0.35 (control 1.9), 0.5 (control 1.10) and 1.23 (control 2.0). Similarly, boiled milk was ineffective in comparison to fresh and pasteurized milk.

The effect of heat at 80 C. on the vitafood diet has already been pointed out (fig. 2). Unheated this diet was highly protective, as only 1 bird in 6 showed a superficial gastric lesion, with an average grade of ulceration for the group of 0.25, and even when 1 per cent cinchophen

14. Almquist, H. J., and Mecchi, E.: Influence of Bile Acids, Vitamin K and Cinchophen on Erosions of the Chick Gizzard Lining, Proc. Soc. Exper. Biol. & Med. **46**:168, 1941.

was added, only 4 of 8 birds showed lesions, with a score of 0.61; all of these lesions were superficial. When this same diet was heated six hours at 80 C., it did not prove more deficient, the grade of ulceration being 0.2 for 10 birds, only 2 showing superficial lesions. However, this heated diet had lost its latent reserve power of protection, for when 1 per cent cinchophen was added lesions developed in all 10 birds, with an average grade of 1.95, which is more than three times as pronounced as when the diet was unheated.

Heating the vitafood diet twenty-four hours at 80 C. proved even more destructive to the protective factor. Lesions developed in 5 of 8 birds on this heated diet without cinchophen. The grade of ulceration was 0.63. When cinchophen was added at the 1 per cent level, all 7 birds in the group fed showed lesions, one of which was of the punched-out type and one was penetrating deeply into the muscular layer. The average score of the lesions was 2.29 to be compared to 0.61 without heat and 1.95 when the period of heating was eighteen hours shorter.

THE PROTECTIVE SUBSTANCE AND CINCHOPHEN ULCERS

It has already been pointed out in discussing the production of gastric ulcers by cinchophen that a certain type of diet, such as vitafood, may be much more protective than another, such as the basal diet containing alfalfa. The efficacy of a few specific food substances in regard to this protective capacity has been noted in a previous communication.[2] It was shown to be present in dried leaves of cereal grasses, canned mixed greens and milk. Further studies along similar lines have been carried out, and the results are recorded in table 1. The majority of food substances tested fall into three general groups: greens and milk; various forms of fresh liver, and stomach extracts.

The effect of dried leaves of cereal grasses was tried out again. It was added at the 5 per cent and the 10 per cent level to the basal diet containing 0.5 per cent and 1 per cent cinchophen. Table 1 shows that it proved protective against both 0.5 and 1.0 per cent cinchophen as compared to the controls but that the 10 per cent level was no more effective than the 5 per cent level. Twenty per cent canned wet spinach was not effective against the basal diet with alfalfa which contained 1.0 per cent cinchophen, although the diet was not relished, and consequently the birds received less cinchophen than the control group. Due to the bulk of the diet, the cinchophen may well have been retained longer and proved more toxic. This is also suggested by the poor gain in weight of this group. Fresh milk in place of water added to the same diet gave good protection as did evaporated milk diluted to its original volume. However, it must be noted that birds allowed to drink milk freely eat less of the diet than

the control birds and consequently receive somewhat less cinchophen. Almquist and associates [15] have recently confirmed the protective properties of milk.

Fresh liver was fed separately from the mash to ten groups of chicks which were receiving 1.0 per cent cinchophen. The liver therapy was started five days before feeding cinchophen and was continued throughout the experiment, usually for a total period of two weeks. The liver was preserved frozen at — 10 C. and only thawed out immediately before it was offered to the birds each day. The dose was 2.5 Gm. per bird in all but 1 experiment, when 10 Gm. per chick was fed. The chick livers used in group S-6-2A were from month old birds which had received 1 per cent cinchophen in the diet for twenty-one days. The dog liver used in group S-3-5 was from 2 adult dogs which had received 0.2 Gm. of cinchophen per kilogram of body weight daily for seventeen and twenty-five days before death, and that used in group S-3-7 was from 2 dogs on the same dose which were killed on the twenty-ninth day of cinchophen feeding.

The normal chick liver was not protective. In the table it looks as if liver from chicks treated with cinchophen might have been protective, as the ulcer score of 2.1 was less than the 2.67 score of the controls. However, the number of birds in group S-6-2A was too small to afford a basis for any such conclusion. It is evident that dog liver is definitely protective, although not strikingly so. The group of chicks receiving 10 Gm. of liver per bird was probably better protected than that receiving 2.5 Gm. and better protected than the table indicates, as 1 per cent of cinchophen was added to the liver in this experiment in addition to that which was added to the mash diet. This addition was considered justifiable as these birds ate proportionately less mash because of the large amounts of meat ingested, but this also meant that more cinchophen was eaten than in the other groups. The two groups of birds fed liver from cinchophen-treated dogs showed no evidence of protection compared to the control group without liver, the ulcer scores being slightly higher, while the birds in this series receiving liver from dogs not treated with cinchophen showed a definite, although slight, reduction in the degree of ulceration. The grade for this series was 1.6 compared to the control grade of 1.95. Group S-1-4 fed human liver appeared to be definitely protected, with an ulcer grade of 0.38 compared to the control of 0.61, but the difference in these figures is not sufficient to make certain of this point without studying a larger group of birds and having a control group with more severe lesions.

15. Almquist, H. J.; Mecchi, E., and Kratzer, F. H.: Effect of Milk on Gizzard Erosion and Cholic Acid in the Chick, Proc. Soc. Exper. Biol. & Med. **47**:525, 1941.

The gastric mucin was fed to the 8 birds in group S-1-7 in table 1 with the expectation that this extract of gastric secretion might prove protective against gastric ulceration in chicks, as such protection has been claimed in treating peptic ulcers in human beings. However, not only did the mucin not prove protective, but the degree of ulceration in group S-1-7 was twice as severe as in the controls. This untoward effect of the mucin might be attributed to its histamine contact, but this particular preparation is presumably histamine free. It may have been constipating, causing greater toxicity from the cinchophen, or the mucin itself may have some unknown toxic properties. It should be studied further.

An experiment with a liquid preparation of gastric secretion made from the fresh mucosa of the pig (gastron) proved interesting in a similar manner. Seventy-five grams of mucosa yields 100 cc. of solution, which contains active pepsin and approximately 0.25 per cent hydrochloric acid. It was supplied in the drinking water, with 3.3 cc. (2.5 Gm. fresh mucosa) allowed per bird per day in 2 experiments, but was offered as a substitute for drinking water in group S-2-2. It proved so toxic for this last group that only 2 birds survived the experiment, and no deductions could be drawn. One of the other two groups was used as a control, while 1 per cent cinchophen was fed to the second. The chicks receiving cinchophen showed a grade of ulceration of 1.35, which was three times as severe as that of the control group given gastron without cinchophen but was also more than twice as severe as that of the control groups given cinchophen without gastron. Evidently, the gastron made the birds more vulnerable to cinchophen ulceration, possibly by increasing the amount of peptic activity of the chicks' stomach contents.

BILE THERAPY

Four years ago Almquist and Mecchi [16] reported the protective action of bile on gizzard erosions. They found that whole bile, fresh or dried; concentrated beef bile; sodium glycocholate; sodium taurocholate; cholic acid, and dehydrocholic acid were all highly effective when fed as 0.5 per cent of the diet. Desoxycholic acid was not nearly so effective, nor was dehydrocholic acid when given by intramuscular injection. Two years ago I tested the protective activity of two commercial preparations of bile salts comprising 2 per cent of the diet. The first, a combination of sodium glycocholate and sodium taurocholate (Fairchild Brothers and Foster), gave complete protection to all 10 birds fed. The second, iron bile salts (bilron, Lilly), gave almost complete protection.

In a further paper in 1941 Almquist and Mecchi [16] confirmed their previous observations on the effect of bile acids on gizzard erosions due

16. Almquist, H. J.: Influence of Bile Acids on Erosions of the Chick Gizzard Lining, Science **87**:538, 1938. Almquist, H. J., and Mecchi, E.: The Influence of Bile on Erosions of the Chick Gizzard Lining, J. Biol. Chem. **126**:407, 1938.

to dietary deficiency and noted the same protective action of bile acids and salts against similar lesions produced by feeding cinchophen. They found a marked increase in cholic acid in the gizzard lining and in the gallbladder bile of birds fed cholic acid but not in those fed types of bile acids other than glycocholic acid. Ox bile salts also produced a high cholic acid content of the chick bile. They concluded that the protective action of certain bile acids, particularly cholic acid, and of bile salts against gastric lesions due to a deficient diet or due to cinchophen is dependent primarily on "bile and especially cholic acid coming in periodic direct contact with the lining serving naturally to aid in maintaining the lining in sound condition."

In 1940 I fed 2 per cent of a combination of sodium glycocholate and sodium taurocholate to a group of 8 chicks receiving 1 per cent cinchophen added to a slightly deficient diet (table 1). Characteristic cinchophen ulcers developed in all but 1 of these birds, and the average score was 2.5. This score was not significantly less than that for the control group, which did not receive cinchophen. It was 2.67. In two subsequent experiments, shown in table 1, 2 per cent cholic acid was added to a protective diet which had given an ulcer score of 0.25. In the first experiment 0.5 per cent cinchophen was also added to the diet and in the second 1 per cent cinchophen. In the first, a lesion developed in only 1 of 6 birds, giving an average score of only 0.33, but the control series of 10 birds for this group, which did not receive cholic acid, had an average score of only 0.15. Similarly, of the 6 birds in the second experiment, lesions developed in 2, giving an average score of 0.92, but the control group had an average score of only 0.61. These experiments with bile salts and cholic acid do not show evidence of any protection against cinchophen gastric ulcers, and this negative result is in accord with a similar one already reported.[2]

These results are just the opposite from those of Almquist and Mecchi, but it should be noted that they used a different method of grading the gastric lesions. Their method is based on the extent of surface involvement and not on the depth of the ulceration. Many penetrating and perforating ulcers occur singly and may be not over 1 to 2 mm. in diameter. This type of lesion would tend to give a low score by their method and a high one by my method. The two cannot justly be compared.

OTHER EFFECTS OF CINCHOPHEN

Cinchophen feeding markedly affects the general nutrition of the bird. The early toxic effects tend to abate somewhat after the second or third day, presumably because the birds eat less per day. One-half per cent of cinchophen produces little or no toxicity, but 1 per cent

cinchophen nearly always affects the birds noticeably. However, in birds taking highly protective diets the signs of toxicity may be completely lacking. This neutralization of the usually encountered toxic signs was complete in the birds receiving 10 per cent dried leaves of cereal grasses cerophyl in the diet and almost complete in the groups receiving 5 per cent dried leaves of cereal grasses, milk and liver. A low grade of gizzard ulceration could be predicted in those birds failing to show signs of toxicity when first offered a diet containing 1 per cent cinchophen.

The birds' appetites were depressed early when fed cinchophen, and this, together with the frequent passage of the characteristic watery mustard-like stools, resulted in slow gain in weight after the first week compared to the control birds which received no cinchophen. If the

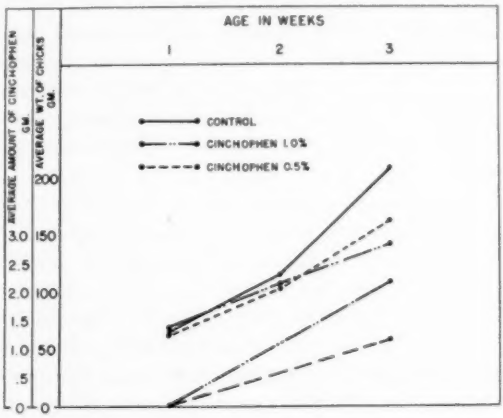

Fig. 7.—The retarding effect of cinchophen fed as 0.5 per cent and as 1 per cent of a vitafood diet on the growth of groups of chicks as shown by a comparison of their average weight curves with that of a normal control group of birds. There were 10 birds in each of the three groups. The lower curves indicate the amount of cinchophen ingested.

chicks were on a deficient diet as well, the retardation in growth was manifest earlier and was more pronounced. The comparative weights at the time of autopsy shown in table 1 show the pronounced variations which may occur with cinchophen therapy and different forms of feed.

The effect of cinchophen on gain in weight is well illustrated in figure 7. Three groups of 10 1 week old chicks were used for this experiment, and all received the highly protective diet vitafood. One group received 0.5 per cent cinchophen in the diet for two weeks; one received 1 per cent cinchophen, and the third served as a control, receiving the diet without cinchophen. The first two groups gained

almost the same amount of weight for the first week, increasing 405 and 388 Gm. respectively, while the control group gained 500 Gm. But by the end of the second week, the group receiving 0.5 per cent cinchophen had gained 600 Gm. more and the group on 1 per cent cinchophen only 360 Gm. more. The control group gained another 930 Gm. for the same period. The amount of cinchophen consumed for the two week period was computed from the amount of diet eaten. All such quantitative determinations are inaccurate in these experiments as an unknown amount of the feed is wasted by the chicks. Nevertheless, the figures of 11.9 and 21.9 Gm. represent a reasonable approximation of the relative amount of cinchophen taken by each of the two groups, based on the first group consuming 2,380 Gm. of feed and the second group 2,190 Gm. The larger amount of cinchophen ingested is clearly associated with a gain in weight in the second week of 40 per cent less than in the other group despite the fact that the dietary consumption was only 8 per cent less for the same period. This indicates that the toxic effect of cinchophen retards growth in some other manner than by depressing appetite and thereby cutting down food consumption. Lehman and Hanzlik [17] came to the same conclusion in 1933 when feeding cinchophen to rats and rabbits.

Possibly an increase in diarrhea may be a factor, as table 1 shows little ulceration occurred in either of these two groups (S-1-1 and S-1-8) despite the lack of satisfactory gain in weight.

No consistent postmortem changes other than ulcers in the gizzard have been found. In a few experiments previously noted [2] gross changes in the liver were observed under special dietary conditions coincident with cinchophen feeding. No histologic evidence of hepatitis or necrosis has been identified, but it should be noted that lethal doses of cinchophen have been avoided and only short time experiments have been carried out. No birds have been treated with this drug longer than one month and most of them for less than two weeks. Further studies of the effects of cinchophen on the liver will be reported at a later date.

THE NATURE OF THE DISORDER

The cause of erosions developing in the lining of the gizzard of chicks fed on a deficient diet is perfectly clear. The birds' food must contain an "anti-gizzard erosion factor," or lining lesions will occur, and an ample supply of this factor in the feed will prevent or clear up lesions. The factor has to do with the normal nutrition of the gastric mucosa in the muscular portion of the stomach. If it is inadequate in amount, mucosal bleeding takes place which may lead to ulceration. As

17. Lehman, A. J., and Hanzlik, P. J.: Cinchophen Toxicosis, Arch. Int. Med. **52**:471 (Sept.) 1933.

the earlier pathologic manifestations of the deficiency are identical with those occurring in birds fed cinchophen and as they may be prevented or cleared up by feeding the same dietary factor, it seems evident that the basic nature of the lesions attributed to cinchophen and those due to a deficient diet will be the same. If this toxic drug interferes with the assimilation of the dietary factor, the gastric mucosa will be deprived of the necessary protective substance just as if it were barred from the diet. There is an excellent precedent for this explanation in two well recognized types of vitamin K deficiency. The diet may be deficient in vitamin K, causing prolonged blood and plasma coagulation times, or severe hepatic damage despite an adequate diet may interfere with the metabolism of vitamin K and cause the same end result—tendency to a fatal hemorrhage.

The possibility of cinchophen causing a toxic effect on the gizzard lining by direct contact must be considered, but this hypothesis does not seem probable for three reasons: First, the initial lesion, bleeding, is beneath the chitinous lining of the gizzard and not at the surface. Second, the early erosive lesion does not develop until one or more days after cinchophen has been introduced. If the drug action was a direct toxic one, lesions should appear earlier. Third, it has been demonstrated in dogs that cinchophen gastric ulcers can be produced by injecting the drug intravenously when no direct contact with the gastric mucosa ever occurs.[18] While administration by this route has not yet been tried in chicks, it is logical to assume that if cinchophen gastric ulcers in dogs (and cats) are produced indirectly, the same mechanism would be applicable to birds. In order to test this hypothesis, 7 birds 3 months old weighing approximately 1 Kg. each were given intraperitoneal injections daily for ten days of a solution of cinchophen containing 0.02 Gm. per cubic centimeter. The conditions and results of this experiment are recorded in table 2. Five of the birds so treated showed definite lesions, with an average ulcer score for the whole group of 1.36. The 5 control birds on the same diets but not receiving cinchophen did not show lesions in the gizzard, giving an ulcer score of 0. Although the groups of birds studied are small, the development of lesions in 71.4 per cent of those receiving cinchophen parenterally contrasted to the absence of lesions in the control group is good evidence that cinchophen gastric ulcers can be produced in chickens without introducing the drug into the stomach. Consequently, until positive proof is offered to the contrary, cinchophen gastric ulcers in chicks may be considered as due to some indirect action of the drug.

18. Stalker, L. K.; Bollman, J. L., and Mann, F. C.: Experimental Peptic Ulcer Produced by Cinchophen; Methods of Production. The Effect of a Mechanical Irritant and the Life History of the Ulcer, Arch. Surg. **35**:290 (Aug.) 1937.

On account of cinchophen's well known capacity for damaging the liver in human beings as well as in experimental animals, the possibility that hepatic damage may be the indirect cause for gastric ulceration in chicks must be explored. The lack of positive histologic evidence for this does not settle this point, as it is readily conceivable that a disorder in hepatic function can occur without morphologic evidence. The beneficial effect of feeding hog liver fat and fresh liver shows that at least liver contains the antiulcer factor, and evidence is presented in table 1 that feeding cinchophen to an animal may destroy this factor. Further support to this theory is offered by a group of birds now under observation which are receiving 5 per cent diethylene dioxide (dioxane) in the drinking water. This substance has a selective toxic action on the

TABLE 2.—*Ulceration in Gizzards of Chicks Following Parenteral Administration of Cinchophen* *

Bird No.	Diet	Amount of Cinchophen	Ulcer Score	Comment
1	Vitafood	5 cc. (0.1 Gm.)	1.5	1 lesion
2	Vitafood	5 cc. (0.1 Gm.)	2.0	2 large lesions
3	Vitafood	5 cc. (0.1 Gm.)	0	Normal
4	Vitafood	None	0	Control, no lesions
5	Vitafood	None	0	Control, no lesions
6	Basal diet	10 cc. (0.2 Gm.)	2.0	3 lesions
7	Basal diet	10 cc. (0.2 Gm.)	1.5	2 small lesions
8	Basal diet	5 cc. (0.1 Gm.)	0	Normal
9	Basal diet	5 cc. (0.1 Gm.)	2.5	3 large lesions
10	Basal diet	None	0	Control, no lesions
11	Basal diet	None	0	Control, no lesions
12	Basal diet	None	0	Control, no lesions

* Each of 7 birds weighing approximately 1 Kg. received ten daily intraperitoneal injections of a solution of cinchophen. Lesions developed in 5. Five control birds did not show any lesions in the gizzard.

liver and kidney.[19] Nine birds were killed between the eighth and the twelfth day of the experiment. All 9 showed gastric ulcerations of the same type as develop when cinchophen is fed. This experiment will be reported on in detail at a latter date. At present it would seem justifiable to assume that cinchophen alters hepatic function and thereby interferes with the normal delivery of the protective substance to the gastric mucosa.

Such a hypothesis would be consistent with the present state of knowledge concerning the administration of bile salts and bile acids. They offer excellent protection against lesions due to dietary deficiency, presumably because they facilitate the absorption of the fat-soluble antierosion factor. They may under certain conditions prove similarly effective against cinchophen gastric ulcers for the same reason, but

19. Fairley, A.; Linton, E. C., and Ford-Moore, A. H.: The Toxicity to Animals of 1-4 Dioxan, J. Hyg. **34**:486, 1934.

if hepatic function is markedly deranged, they may prove ineffectual, as the factor could not be properly utilized, even though it was absorbed in sufficient amount.

Whatever the *modus operandi* of this fat-soluble antierosion factor, it would seem desirable for the sake of convenience, both for brevity and specificity, to designate it as a vitamin and in view of its antiulcer properties to call it vitamin U. Its characteristics are now so well recognized in experiments on chicks that such terminology would appear to be entirely justifiable.

THE PEPTIC ULCER PROBLEM IN HUMAN BEINGS

The gastric ulcers in chicks which have been described as due to a dietary deficiency or to the ingestion of cinchophen or to a combination of both present striking similarities to the peptic ulcers occurring so commonly in human beings. However, there is at present absolutely no positive evidence that the mechanism of production of ulcers in the gizzards of birds is related to the problems of the etiology of peptic ulcers in human beings. Nevertheless, certain similarities cannot be overlooked as offering a new type of evidence that a conditioned nutritional deficiency may be a factor in precipitating the primary lesion in the development of peptic ulcers in patients.

At present it will suffice to point out that ulcers in chicks are always in the muscular part of the stomach where highly acid gastric juice rich in pepsin first strikes the wall and that macroscopically and microscopically they have the characteristics of peptic ulcers developing in animals or man. Similarly, gastric ulcers have been dsecribed in dogs, cats [20] and even human beings [21] after the administration of cinchophen. Also the clinical evidence of peptic ulcer varies in certain groups of people or in nations related to the type of diet consumed,[22] and Fanley and Ivy [23] have shown that a special diet can reduce the incidence and modify the severity of experimentally produced jejunal ulcers in dogs.

20. Van Wagoner, F. H., and Churchill, T. P.: Production of Gastric and Duodenal Ulcers in Experimental Cinchophen Poisoning in Dogs, Arch. Path. **14**: 860-869 (Dec.) 1932. Schwartz, S. O., and Simonds, J. P.: Peptic Ulcers Produced by Feeding Cinchophen to Mammals Other than the Dog, Proc. Soc. Exper. Biol. & Med. **32**:1133-1134, 1935. Simonds, J. P.: Mode of Origin of Experimental Gastric Ulcer Produced by Cinchophen, Arch. Path. **26**:44 (July) 1938. Stalker, Bollman and Mann.[18]

21. Reah, T. G.: Cinchophen Poisoning, Lancet **2**:504, 1932. Bloch, L., and Rosenberg, D. H.: Gastric Ulcers Associated with Cinchophen Poisoning, Am. J. Digest. Dis. & Nutrition **1**:29, 1934.

22. Alsted, G.: Studies of the Changing Incidence of Peptic Ulcer of the Stomach and Duodenum, London, Oxford University Press, 1939, p. 20.

23. Fanley, G. B., and Ivy, A. C.: The Prevention of Postoperative Jejunal Ulcers by Diet and Fundusectomy, Surg., Gynec. & Obst. **63**:717, 1936.

The initial lesion in chicks is bleeding, which corresponds to recent gastroscopic observations on human subjects,[24] and the development of the ulcer may be furthered by increasing the hydrochloric acid and pepsin concentration in the gastric contents as shown by feeding gastron. The beneficial effect of milk on gastric ulcers in birds has a well known counterpart in patients with ulcer. The experiments on birds suggest a vitamin factor as responsible for the therapeutic efficacy of milk rather than its liquid form and show that this factor is destroyed by heat.

There is considerable evidence that a disturbance in hepatic function can be responsible for the development of peptic ulcers in chicks. Such a disturbance has also been held responsible for the appearance of ulcers in the stomachs of dogs fed cinchophen,[25] and it has been suggested that there is a clinical relation between altered hepatic function and peptic ulcers in patients.[26] Whether such comparisons between the erosive and ulcerative lesions of birds' gizzards and peptic ulcer in human beings may prove entirely illusionary must depend on the results of future investigations, but the marked similarities between the peptic ulcers of birds and of patients suggest a relation which must be disproved by experimentation before it can be disregarded.

SUMMARY

1. It has been demonstrated repeatedly in the last five years that superficial ulcers (erosions) develop in the gizzards of chicks which are fed on a deficient diet. The deficiency is due to the lack of a specific substance termed the anti-gizzard-erosion factor and can be prevented or cured by the addition of this factor to the diet.

2. This factor is fat-soluble, is contained in the sterol fraction of fat which is saponifiable and is readily destroyed by heat. It occurs in close association with, but is definitely separate from, vitamin K and is present in alfalfa, many cereals, liver, fish oils, fresh milk and a variety of other substances.

3. The same type of lesion can be produced in the muscular portion of the chick's stomach by the administration of cinchophen either orally

24. Schindler, R.: Chronic Localized Gastric Purpura, Am. J. Digest. Dis. **5**:796, 1939.

25. Reymont, A.: A Study of Liver Function in Experimental Peptic Ulcer, Am. J. Digest. Dis. **1**:65, 1940.

26. Vilardell, J., and Corachán Llort, M.: Estudio histológico del hígado (por biopsia) en las colecistitis y ulcus gastro-duodenal, Rev. méd. de Barcelona **17**: 225, 1932. Jergesen, F. H., and Simonds, J. P.: The Blood Lipase in Patients with Peptic Ulcer, J. Lab. & Clin. Med. **19**:1054, 1934. Schnitker, M. A., and Hass, G. M.: A Histological Study of the Liver in Patients Affected with Peptic Ulcer, Am. J. Digest. Dis. & Nutrition **1**:537, 1934.

or parenterally, and increased amounts of this toxic drug will produce more pronounced and even penetrating and perforating ulcers. These ulcers tend to heal rapidly when cinchophen feeding is stopped.

4. Cinchophen gastric ulcers in chicks are more pronounced the more deficient the diet and grossly and histologically resemble peptic ulcers in human beings. Only acute and subacute lesions have been studied to date.

5. As the same dietary factor evidently prevents or modifies gastric ulcers due to cinchophen that prevents dietary deficiency ulcers, it is suggested that this factor be designated as vitamin U because of its proved antiulcer properties in the chick.

6. Certain bile acids and bile salts will prevent the development of deficiency ulcers in chicks and may have a similar beneficial effect on cinchophen gastric ulcers. This observation is best explained by assuming that bile promotes the intestinal absorption of the fat-soluble factor.

7. It seems probable that the ulcer-producing properties of cinchophen are due not to direct action on the lining of the stomach but to an indirect effect on the liver. Damage to the liver may then interfere with the elaboration and storage of the antiulcer factor and its delivery to the stomach wall. There are a number of independent observations in the literature on ulcers in dogs and in patients to support such a hypothesis.

8. There is at present no proved relation between this antiulcer factor and the problem of the etiology of peptic ulcer in human beings. There is, however, much to justify a critical survey of the clinical problem before dismissing the possibility of such a relation.

210 Post Street.

TREATMENT OF PNEUMONIA WITH SULFATHIAZOLE

ALVIN E. PRICE, M.D.
AND
GORDON B. MYERS, M.D.
DETROIT

Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) has been widely used for the treatment of pneumococcic pneumonia during the past two years. There are numerous reports attesting to its value, but only one series [1] exceeding 250 cases has been described to date. The following report is based on 557 cases of pneumonia in which treatment was with sulfathiazole.

METHOD

Diagnosis.—The cases included in this study represent all patients over 12 years of age with pneumonia who were admitted to the pneumonia services of the City of Detroit Receiving Hospital and the William J. Seymour Hospital, Eloise, Mich., between Jan. 1, 1940 and Aug. 1, 1941 and who were treated with sulfathiazole. The diagnosis was confirmed by roentgenogram in every case. On admission sputum was typed directly by the Neufeld method, and the results were checked either by mouse inoculation or by the direct typing of a second specimen. Typing was repeated in the event of an extension. Blood cultures were made on admission and were repeated daily. Hemoglobin estimations, white cell counts and differential counts were made frequently during therapy. Red cell counts were made routinely at the beginning and at the end of treatment.

Dose of Sulfathiazole.[2]—The dose administered depended on the severity of illness. In the vast majority of cases (420) an initial dose of 60 grains (4 Gm.) was given by mouth and followed by 15 grains (1 Gm.) every four hours around the clock (six times daily) until the temperature remained normal for twenty-four to forty-eight hours. In a limited number of cases (51) doses one-half as large as those just mentioned were given. In 71 cases in which the patients were critically ill an initial dose of 60 grains (4 Gm.) of sodium sulfathiazole was given intravenously. In most instances this dose was repeated two hours later. Thereafter, in these cases the patients received sulfathiazole orally or the sodium salt intravenously in doses of 15-30 grains (1-2 Gm.) every four hours until convalescence was established. Type-specific antipneumococcus serum was given as a supplement in 23 cases in which the patients were critically ill and in which the causative pneumococci were distributed by type as follows: type I, 5 cases;

From the Department of Medicine, Wayne University College of Medicine.

1. Schwartz, L., and Flippin, H. F.: Sulfathiazole in the Treatment of Pneumonia, Pennsylvania M. J. **44**:446, 1941.

2. Most of the sulfathiazole used in this study was furnished by E. R. Squibb and Sons and Merck and Company.

TABLE 1.—*Summary of Pertinent Data in Five Hundred and Fifty-Seven Cases of Pneumonia in Which Treatment Was with Sulfathiazole*

Type of Causative Pneumococcus	Age, Yr.							Duration of Therapy, Hr.		Consolidation			Blood Culture Colony Count				White Cell Count Below 6,000 per Cu. Mm.	Total No. of Cases	No. of Deaths
										Lobar Pneumonia		Bronchopneumonia							
	10-19	20-29	30-39	40-49	50-59	60-69	70+	<96	>96	1 Lobe	2 Lobes or More		N. D.*	<10	10-100	100+			
I	1	14(1)†	19	11	8(2)	6(2)	2(1)	33(2)	24(3)	44(4)	14(2)	3	3(1)	12(1)	2	1	0	61	6
II	2	4	8(1)	6	10(2)	2	1(1)	22(2)	7(1)	18(1)	13(3)	2	1	5(1)	1	3(2)	4(1)	33	4
III	3	3	6	8(2)	8(3)	7(4)	7(2)	21(4)	14(4)	21(5)	14(6)	7	0	3(1)	0	4(4)	5(3)	42	11
IV	5	7(1)	6(1)	10	9(1)	6	2	26(1)	10(1)	21	15(3)	9	3	4	1(1)	0	3(1)	45	3
V	1	5	5	2(1)	2	1	2(1)	10(1)	8(1)	10	7(1)	1(1)	1	3	1	2(1)	0	18	2
VI	1	1	3(2)	2	3(1)	3	4	11	5(2)	7	3(2)	7(1)	0	1(1)	0	1(1)	1(1)	17	3
VII	8	7	9(2)	8(1)	4(1)	1	0	24(1)	10(2)	17(2)	17(2)	3	5	2	3	3(2)	5(1)	37	4
VIII	2	5	3	5(2)	9(1)	3(1)	4(1)	23(3)	5(2)	17(1)	4(2)	10(2)	1	3(1)	0	1(1)	1(1)	31	5
IX	0	0	3	1	3	2	0	6	2	4	3	2	0	1	0	0	0	9	0
X	0	1	3	2	4	1	1	6	4	7	2	3	2	1	0	0	0	12	0
XI	1	0	2	0	1	2	1(1)	6(1)	0	4	0	3(1)	0	0	0	0	0	7	1
XII	0	2	2(1)	1	2	0	1(1)	5(1)	2(1)	5	1(1)	2(1)	1(1)	1	0	0	0	8	2
XIII	0	1	4	2	1	3	0	5	4	8	0	3	0	0	0	0	0	11	0
XIV	0	0	1	0	1	1	0	2	0	3	0	0	0	0	0	0	0	3	0
XV	1	0	1	4(1)	0	0	0	4	2(1)	1	1(1)	4	0	1	0	0	1	6	1
XVI	1	1	1	2	2(1)	1	0	3	3	5	1	2(1)	0	0	0	0	0	8	1
XVII	0	2	4	1	3	0	1	6	3	4	2	5	0	0	0	0	0	11	0
XVIII	3	3	4	3	0	0	2(1)	9(1)	2	6	3	6(1)	0	1	0	0	1	15	1
XIX	1	1	3	2(1)	5	1	0	8	4(1)	10	1	2(1)	0	0	1	0	2	13	1
XX	1	2	4(1)	3	4	3	0	12(1)	1	9	2	6(1)	0	1(1)	0	0	2	17	1
XXI	1	1	1	2	1	2	0	7	3	4	0	4	0	0	0	0	1	8	0
XXII	1	1	2	2	1	0	0	5	0	4	0	2	0	0	0	0	0	7	0
XXIII	0	0	1	2	3	1	0	3	1	3	3	1	1	0	0	0	0	7	0
XXIV	0	0	0	0	2	1	2	2	0	2	2	1	0	1	0	0	1	5	0
XXV	0	2	0	2	4(2)	0	1(1)	5(1)	3(1)	2	5(3)	0	2(1)	0	1	2(2)	1(1)	7	3
XXVI	0	0	0	1	0	2	0	2	1	1	0	2	0	0	0	0	0	3	1
XXVII	0	1	0	0	1	0	1(1)	0	3	2	1	1	0	2	0	0	0	4	1
XXIX	0	2	0	0	2	2	0	5(1)	1	3	2	3	0	0	0	0	0	11	1
XXXI	0	0	0	1	0	2	0	3	0	2	1	0	0	0	0	0	0	3	0
XXXII	1	1	1	2	0	2	0	3	2	4	3	0	1	1	0	0	0	7	0
XXXIII	1	3	2(1)	0	0	1(1)	0	6(1)	1(1)	6(1)	1(1)	0	1(1)	0	1(1)	0	1(1)	7	2
No pneumococci	8	8	19(1)	15(1)	12(1)	6(2)	15(4)	45(3)	12(2)	38(1)	8(3)	37(5)	0	0	0	0	5(1)	83	9
Pneumococcus not typable	0	1	1	1	0	0	0	1	0	1	0	2	0	0	0	0	1	3	0
Total	44	76 (2)	120 (11)	104 (10)	106 (15)	58 (10)	49 (15)	325 (25)	135 (23)	291 (17)	129 (30)	137 (16)	22 (4)	42 (7)	11 (2)	17 (13)	35 (11)	557	63

* N. D., blood culture positive for pneumococci; colony count not done.
† The figure in parentheses indicates the number of deaths.

type II, 6 cases; type III, 5 cases; type IV, 2 cases; type V, 1 case, and type VII, 4 cases. During the early part of the study an equal amount of sodium bicarbonate was given with each dose of sulfathiazole. Since this was found inadequate for alkalinization of the urine, the dose was later increased to one teaspoonful. The level of sulfathiazole in the blood was determined within twenty-four hours of the beginning of medication and daily thereafter.

SUMMARY OF CASES

Age, Sex and Race.—The age distribution is given by decade in table 1. In more than one half of the cases (57 per cent) the patients were over 40 years of age. The proportion of males was 78 per cent. The race distribution was as follows: white patients, 63 per cent, Negro patients, 37 per cent.

Type and Severity of Pneumonia.—Most of the significant data are summarized in table 1. The interval between the onset of pneumonia and the beginning of chemotherapy exceeded ninety-six hours in 29 per cent of the cases. The pneumonia was classified as lobar in 75 per cent of the cases. More than one lobe was involved in 31 per cent of this group. Pneumococcic bacteremia was present in 19.4 per cent of cases of pneumococcic pneumonia (16.3 per cent of the entire series). Colony counts were done in 60 cases of bacteremia, and over 100 organisms per cubic centimeter were found in 28 per cent. The leukocyte count on admission was below 6,000 in 35 cases (6 per cent) and was between 6,000 and 10,000 in 78 additional cases (14 per cent).

Associated Diseases.—A history of daily consumption of large amounts of alcohol was obtained in 97 cases (17 per cent), in many of which the patients were admitted in delirium tremens. In a total of 38 cases there was definite clinical evidence of congestive heart failure; in 36 others there was compensated organic heart disease. Cirrhosis was encountered in 8 cases; toxic hepatitis was present on admission in 3 others, and moderate to marked azotemia was present before therapy in a total of 18 cases. There were 6 cases of diabetes mellitus, 9 cases of a malignant growth, 9 cases of chronic pulmonary tuberculosis and 21 cases of chronic asthmatic bronchitis or bronchiectasis. Empyema was present on admission in 5 instances. The pneumonia was secondary to chest injury in 12 cases and followed operation in 36.

RESULTS

Fatality Rate.—The uncorrected fatality rate for the entire series of 557 cases was 11.3 per cent. The fatality rate by decade was as follows: second decade, 0; third, 2.6 per cent; fourth, 9.1 per cent; fifth, 9.6 per cent; sixth, 14.1 per cent; seventh, 17.2 per cent, and eighth and over, 30.6 per cent. In those cases in which treatment with sulfathiazole was started within ninety-six hours of the onset of pneumonia the fatality rate

was 7.6 per cent; in the remainder it was 17.0 per cent. There were 5.8 per cent deaths in the cases of lobar consolidation confined to one lobe, 23.2 per cent deaths in cases of consolidation of two or more lobes and 11.6 per cent deaths in cases of bronchopneumonia. The fatality rate for all 92 cases of bacteremia was 28.2 per cent. A breakdown of these figures according to colony count gave the following results: less than 10 organisms per cubic centimeter, 16.6 per cent deaths; 10 to 100 per cubic centimeter, 18.2 per cent deaths, and over 100 per cubic centimeter, 76.4 per cent deaths.

Analysis of Deaths.—An analysis of the deaths is presented in table 2. In 19 cases death occurred within twenty-four hours of the institution of sulfathiazole therapy. If these cases were excluded, the corrected fatality rate would be 8.1 per cent. In 24 additional cases the patients were considered to have terminal pneumonia complicating serious debilitating disease (such as cardiac failure or uremia). If these were also excluded, the corrected fatality rate would be 3.9 per cent. In 3 cases death was due to empyema or abscess of the lung, and in 3 it was due to pneumococcic endocarditis. In at least 1 of the latter the endocarditis was probably present on admission. In 5 cases fatal extension developed after apparent response to chemotherapy. In 1 case (60) an extension of the patient's pneumonia caused by pneumococci of type I and a blood culture positive for these organisms developed during the administration of sulfathiazole. The organisms recovered from the blood stream were resistant to sulfathiazole in vitro, growing in mediums containing 20 mg. per hundred cubic centimeters. In 1 case death from circulatory collapse followed the administration of epinephrine. Toxic reactions from sulfathiazole were a major factor in death in 2 cases. In 1 of these cases (61) the patient died in anuria after exfoliative dermatitis. In the other case (63) the patient showed numerous acetylsulfathiazole calculi in both kidneys at autopsy.

Clinical Effects.—The temperature fell to normal within twenty-four hours of the institution of sulfathiazole therapy in 145 cases (26 per cent) and within forty-eight hours in a total of 288 cases (51.7 per cent). The concentration of free sulfathiazole in the blood was determined at defervescence in 299 cases. It was below 2 mg. per hundred cubic centimeters in 83 cases, between 2 and 4 mg. in 124 cases, between 4 and 6 mg. in 59 cases and over 6 mg. in 33 cases. The temperature fell by crisis in many cases in which the blood levels of sulfathiazole consistently were between 1.5 and 3 mg. per hundred cubic centimeters. The blood culture became negative for pneumococci in 76 of the 92 cases of bacteremia (82.6 per cent). In most instances this occurred within twelve to twenty-four hours of the institution of chemotherapy. In 10 cases in which the blood culture became negative the patients died sub-

TABLE 2.—*Analysis of Deaths*

Case No.	Type of Pneumococcus	Age, Yr.	Blood Culture, Colonies per Cc.	No. of Lobes Involved	White Cells per Cc.	Duration of Therapy	Total Dose, Grains	Serum, Units	Comment
					Overwhelming Infection, Death Within 24 Hours				
1	I	90	1	2	.....	11 hr.	150	.....	Aged 90
2	II	59	6	3	6,300	17 hr.	150	600,000	Postoperative perforated peptic ulcer
3	II	56	5,000	3	3,100	10 hr.	120	180,000	
4	II	33	1,900	2	6,100	16 hr.	180	200,000	Delirium tremens on admission; peripheral circulatory collapse; autopsy showed toxic myocarditis
5	III	68	5,000	2	10,200	9 hr.	135	.....	Arteriosclerotic heart disease
6	III	49	0	2	2,900	9 hr.	120	100,000	Delirium tremens and empyema on admission
7	III	49	600	1	1,000	9 hr.	150	170,000	Delirium tremens; extreme leukopenia
8	III	52	0	2	7,900	20 hr.	180	100,000	
9	III	56	780	1	14,200	5 hr.	120	80,000	
10	III	67	1	2	15,000	11 hr.	240	360,000	Autopsy: coronary sclerosis with old myocardial infarct; death from pneumonia
11	VI	37	6	2	9,400	7 hr.	90	.....	Delirium tremens; hepatitis (icterus index 115)
12	VII	56	6,000	3	5,600	9 hr.	165	280,000	In circulatory collapse on admission
13	VII	39	0	1	15,400	18 hr.	120	.....	Delirium tremens
14	VII	44	7,000	4	2,700	7 hr.	150	200,000	
15	VIII	47	1,900	2	1,300	8 hr.	120	.....	Delirium tremens
16	XXV	51	5,000	3	2,400	18 hr.	240	.....	
17	XXXIII	38	40	3	2,200	15 hr.	195	.....	Blood culture sterilized before death
					Overwhelming Infection, Death Within 48 Hours				
18	III	61	180	3	3,500	25 hr.	165	.....	Blood culture sterilized before death
19	IV	57	0	3	3,300	24 hr.	270	100,000	
20	IV	27	25	4	6,300	28 hr.	225	300,000	Delivery (full term) in hospital; empyema on admission
21	V	46	183	4	28,200	48 hr.	315	100,000	Delirium tremens; blood culture sterilized before death
					Terminal Pneumonia, with Serious Associated Disease				
22	I	52	0	1	16,400	19 hr.	60	.....	Right bundle branch block, cirrhosis; death 19 hr. after sulfathiazole started, but dosage inadequate
23	I	56	0	1	22,500	14 hr.	120	.....	Delirium tremens; cardiac failure
24	I	64	0	1	28,400	3.5 days	220	.....	Cardiac failure and uremia (blood urea 312 mg./100 cc.); temperature normal for 3 days before death; no autopsy
25	II	80	0	1	14,300	1.5 days	195	.....	Hypertension with cardiac failure
26	III	67	0	1	12,500	5 days	465	.....	Coexistent moist arteriosclerotic gangrene of leg
27	III	72	0	1	10,400	6 days	510	.....	Cardiac failure; temperature normal for 6 days before death; clinical impression was that pneumonia had cleared up; no autopsy
28	V	76	0	1	11,000	19 days	1,245	.....	Failure of right side of heart; temperature normal for 5 days before death; no autopsy
29	VIII	73	0	2	23,400	3.5 days	375	.....	Comatose and in circulatory collapse on admission; autopsy showed coronary sclerosis, myocardial fibrosis, acute myocarditis and acute fibrinous pericarditis
30	VIII	40	0	3	13,000	3 days	285	.....	Delirium tremens throughout stay in hospital
31	VIII	64	0	2	22,700	5 days	540	.....	Blood urea 164 mg./100 cc. on admission; aortic insufficiency; chronic asthmatic bronchitis
32	XI	72	0	2	10,600	5 days	525	.....	Hypertension with left ventricular failure; no therapeutic response
33	XII	30	0	2	19,700	4 days	615	.....	In circulatory collapse on admission; autopsy revealed severe chronic pyelonephritis, cardiac hypertrophy and secondary pneumonia caused by hemolytic streptococcus
34	XV	47	0	2	21,800	13 days	975	.....	Laminectomy for epidural abscess; chronic pyelonephritis
35	XVI	50	0	1	12,200	2 days	200	.....	Korsakoff's psychosis
36	XIX	40	0	1	19,100	25 hr.	120	.....	Six months' pregnancy; mild pneumonia with favorable progress until advent of spontaneous abortion; circulatory collapse during delivery; death shortly afterward
37	XX	39	1	3	32,400	2 days	170	.....	Acute glomerulonephritis with uremia, hypertensive encephalopathy and terminal left ventricular failure; blood culture sterilized; death
42	No pneumococcus	76	0	2	35,700	7 days	705	.....	Fracture of neck of femur; arteriosclerotic heart disease with failure
43	No pneumococcus	73	0	2	19,500	7 days	660	.....	Chronic pulmonary tuberculosis; arteriosclerotic heart disease; bronchiectasis

37	XX	39	1	3	32,400	2 days	170	.....	Acute glomerulonephritis with uremia, hypertensive encephalopathy and terminal left ventricular failure; blood culture sterile(?); death advent of spontaneous abortion; circulatory collapse during delivery; death shortly afterward
42	No pneumococcus	76	0	2	35,700	7 days	705	.....	Fracture of neck of femur; arteriosclerotic heart disease with failure
43	No pneumococcus	73	0	2	10,500	7 days	660	.....	Chronic pulmonary tuberculosis; arteriosclerotic heart disease; bronchiectasis
44	No pneumococcus	48	0	2	4,300	5 days	465	.....	Delirium tremens; extreme dyspnea and cyanosis disproportionate to pulmonary signs and suggestive of pulmonary embolism; no autopsy
45	No pneumococcus	70	0	2	16,000	9 days	690	.....	Fracture of tibia and fibula; arteriosclerotic heart disease with failure
46	No pneumococcus	60	0	1	15,500	1.5 days	165	.....	Delirium tremens; congestive heart failure
47	No pneumococcus	56	0	2	20,500	1.5 days	165	.....	Cerebral hemorrhage with hemiplegia
					Death from Complications of Pneumonia				
48	III	59	0	2	12,100	6 days	510	.....	Abscess of lung and empyema; death after operation
49	VI	52	102	2	9,100	4 days	555	.....	Autopsy showed vegetative endocarditis caused by pneumococci of type VI superimposed on rheumatic aortic stenosis
50	VI	36	0	3	4,900	9 days	840	.....	Chronic alcoholism; admitted in barbital coma; empyema developed; death from cellulitis caused by hemolytic streptococcus
51	VIII	57	1	1	6,900	5 days	495	.....	Chronic alcoholism; admitted in coma; blood culture sterilized; autopsy showed multiple abscesses of lung
52	XXV	71	+	3	11,500	22 days	2,545	.....	Autopsy showed vegetative endocarditis caused by pneumococci of type XXV
53	XXV	50	350	3	14,700	5 days	450	.....	Aortic insufficiency 24 hr. after sulfathiazole started; autopsy showed vegetative endocarditis caused by pneumococci of type XXV
					Therapeutic Failure, Death from Extension or Drug Resistance				
54	IV, VI, XVII	36	0	2	17,000	4 days	375	.....	After 3 days' normal temperature extension developed; autopsy showed chronic pyelonephritis, productive pulmonary tuberculosis with terminal pneumonia; no pneumococci in lung at autopsy
55	XVII, VIII, XII	71	0	2	17,900	6 days	510	.....	After 4 days of normal temperature with apparent recovery from original pneumonia, consolidation caused by pneumococci of type XII and bacteremia developed; blood culture sterilized before death
			1	2	18,000	1.5 days	210	.....	
56	XVIII	82	0	2	9,100	8 days	795	.....	After 2 days of normal temperature, extension developed; no pneumococci in sputum; no response to second course of sulfathiazole
57	XXIX	34	0	1	13,500	3 days	300	.....	Lymphatic and splenic tuberculosis; after 2 days of normal temperature with roentgen evidence of resolution of original pneumonia, fever recurred; autopsy revealed diffuse terminal bronchopneumonia
58	No pneumococcus	87	0	1	10,900	5 days	510	.....	Terminal pneumonia with temporary response to chemotherapy, then a fatal relapse
59	I	28	+	4	21,300	7 days	675	.....	Extensive pneumonia with marked cyanosis and dyspnea; blood culture sterilized before death from pneumonia
60	I	67	0	1	18,300	4 days	390	.....	Complete therapeutic failure; drug resistant; organisms grew in media containing 20 mg./100 cc. of sulfathiazole; pneumonia extended and blood culture became positive during sulfathiazole therapy; subsequently 720,000 units of antipneumococcus serum and hydroxyethylapocupreine given without clinical effect
					Death Due Principally to Reaction to Therapy				
61	III	70	0	1	14,700	6 days	525	.....	Drug fever, conjunctivitis, exfoliative dermatitis and anuria developed; death in uremia; pneumonia completely resolved at autopsy; cirrhosis, nephrosclerosis and cardiac hypertrophy encountered; no calculi or crystals encountered in kidneys, but sulfathiazole considered a major factor in death
62	VII	38	0	1	20,000	36 hr.	180	.....	Underlying asthma; 5 minims (0.31 cc.) of a 1:1,000 solution of epinephrine hydrochloride given; ten minutes later circulatory collapse (blood pressure unobtainable); revival by plasma transfusions, desoxycorticosterone acetate, etc. unsuccessful; autopsy showed marked cerebral hyperemia and small intraventricular hemorrhage
63	No pneumococcus	39	0	2	18,400	5 days	555	.....	Chronic osteomyelitis; death in uremia; autopsy revealed many small acetylsulfathiazole calculi in both kidneys, also acute glomerulotubular nephritis thought to be due to sulfathiazole; pneumonia unresolved

sequently. There was clinical and roentgen evidence of extension of the pneumonia during therapy in 35 cases. This included extension within the originally involved lobe as well as spread to other parts of the lung. Resolution was delayed beyond three weeks in 14 cases.

Complications.—The incidence of suppurative complications was low. Empyema developed in 6 cases (1 per cent), in all of which surgical therapy was required. There were 2 cases of abscess of the lung, both proved at necropsy. Suppurative arthritis of the shoulder developed in 1 case. The joint continued to drain profusely for one month after surgical incision, at which time direct instillation of sulfathiazole paste was begun. There was a prompt reduction in the amount of discharge,

TABLE 3.—*Toxicity of Sulfathiazole*

Type of reaction	Percentage
Gastrointestinal reaction	
Severe nausea and vomiting	1.8
Mild nausea and vomiting	9.6
Cerebral reaction	
Severe (delirium or convulsions)	0.7
Mild (headache, dizziness, drowsiness)	7.4
Drug fever	
Definite	7.6
Questionable	2.0
Lesions of the skin and mucous membrane	
Conjunctivitis	1.8
Dermatitis (usually papular or nodular)	3.7
Hematopoietic reaction	
Hemolytic anemia	0.2
Fall in hemoglobin exceeding 2 Gm./100 cc.	5.9
Leukopenia (3,000-5,000 cells)	1.8
Reaction in the urinary tract	
Microscopic hematuria	9.4
Acetylsulfathiazole calculi	0.2
Renal insufficiency	0.9
Reaction in the liver	
Jaundice	0.2

and with supplementary physical therapy a good functional result was obtained. There were 3 cases of fibrinous pericarditis. The diagnosis was based on a characteristic pericardial friction rub and was confirmed at autopsy in 1 instance. In the other 2 cases the patients recovered under sulfathiazole therapy without a clinically recognizable effusion developing. There were 3 cases of acute bacterial endocarditis, all proved at necropsy. In 1 of these cases the patient had terminal pneumococcic meningitis. Secondary bacteremia caused by Streptococcus haemolyticus developed in 4 cases, in 3 of which the patients died. In 1 additional case a patient had an associated bacteremia caused by Staphylococcus aureus but recovered.

Toxic Manifestations.—The incidence of toxic manifestations among the 538 cases in which treatment was with sulfathiazole for a minimum

of twenty-four hours is given in table 3. Nausea and vomiting sufficiently severe to interfere with administration of sulfathiazole were present in only 10 cases. In 1 case a patient had several epileptiform convulsions in association with a blood level of sulfathiazole above 15 mg. per hundred cubic centimeters. After the concentration of this compound in the blood fell below this figure, there were no further convulsions and a complete recovery was made. There were 3 instances of toxic psychosis, in which sulfathiazole was considered a major contributory factor. Mild cerebral symptoms, such as headache, dizziness and drowsiness were recorded in 40 cases. In some instances, however, these symptoms probably resulted from pneumonia rather than from therapy. Drug fever was a fairly common complication in those cases in which sulfathiazole was administered for more than four days. All types of temperature curve were observed. Before we accepted a diagnosis of drug fever, every effort was made to exclude extension and complications of pneumonia. Undoubted drug fever occurred in 7.6 per cent of the cases. Dermatitis developed in approximately one half of the cases of drug fever. The most common varieties were a papular dermatitis involving the hands and face and erythema nodosa–like lesions involving the extremities. Conjunctivitis was present in approximately one fourth of the cases of drug fever. A drop in hemoglobin of more than 2 Gm. per hundred cubic centimeters occurred during the course of therapy in 33 cases. In only 1 of these was the drop of sufficient magnitude and rapidity to warrant the diagnosis of acute hemolytic anemia. In this case, the hemoglobin fell 4 Gm. per hundred cubic centimeters and the red cell count fell 1,100,000 cells per cubic millimeter during the course of six days. The white cell count fell below 5,000 per cubic millimeter during the course of therapy in 10 cases, the lowest count being 2,600 per cubic millimeter. Mild jaundice developed in 1 case during the course of therapy. Microscopic hematuria, exceeding 10 red cells per high power field, occurred in 9.4 per cent of the cases. The hematuria tended to appear when the urine was acid and the output low and to disappear when fluids were forced and the urine was alkalinized. Fatal uremia developed in 2 cases during therapy. In 1 of these (case 61) the patient died in anuria complicating a sulfathiazole exfoliative dermatitis. Autopsy in the other (case 63) revealed many small acetylsulfathiazole calculi in both kidneys together with an acute glomerulotubular nephritis, which was thought to be due to the drug. In 3 additional cases renal insufficiency of lesser degree developed.

COMMENT

The results of sulfathiazole therapy recorded here were distinctly superior to those previously obtained with sulfanilamide or with sulfa-

pyridine (2-[paraaminobenzenesulfonamido]-pyridine) at the same institutions. The uncorrected fatality rates in cases of roentgenographically proved pneumonia in patients over 12 years of age were as follows: sulfanilamide (369 cases), 23.8 per cent; sulfapyridine (139 cases), 18.7 per cent, and sulfathiazole (557 cases), 11.3 per cent. The corrected fatality rates, excluding deaths occurring within twenty-four hours of the institution of chemotherapy, were 21.1, 18 and 8.1 per cent, respectively. The fatality rates for pneumococcic bacteremia treated with each of the three drugs was as follows: sulfanilamide (73 cases), 48 per cent, sulfapyridine (32 cases), 37.5 per cent, and sulfathiazole (92 cases), 28.2 per cent. A more detailed comparative study, including results of therapy with sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) will form the subject of a future communication.

SUMMARY

The results of sulfathiazole therapy in 557 cases of pneumonia in adults are presented and analyzed from the standpoint of the type of causative Pneumococcus, the age of the patient, the duration of the pneumonia, the extent of the consolidation, the blood culture, the initial white cell count, associated diseases and complications. The uncorrected fatality rate was 11.3 per cent. A tabular analysis of all deaths is included. The incidence of bacteremia was 16.3 per cent, and the fatality rate was 28.2 per cent. Defervescence occurred within forty-eight hours of the institution of sulfathiazole therapy in 51.7 per cent of cases. The incidence of suppurative complications was low. Serious toxic reactions from sulfathiazole were uncommon but were considered a major factor in death in 2 cases. The results of sulfathiazole therapy were superior to those previously obtained with sulfanilamide or with sulfapyridine.

1553 Woodward Avenue.

City of Detroit Receiving Hospital.

MECHANISM OF PENTOTHAL SODIUM ANTIDIURESIS

HERBERT SILVETTE, PH.D.
CHARLOTTESVILLE, VA.

Extensive studies of the effects of barbiturates on renal function are few. Epstein investigated the influence of certain barbiturates on diuresis in rabbits caused by thyroxin [1] and by sodium chloride.[2] In 1930 Ogden [3] described the action of amytal in inhibiting water diuresis in dogs during anesthesia, an observation which has been confirmed in many teaching laboratories. Walton [4] and Gouax, Cordill and Eaton [5] did not observe any significant effect of sodium amytal on the twenty-four hour output of urine, though this is rather misleading, since suppression of renal activity during a short period of anesthesia was compensated for by subsequent diuresis. It is, moreover, generally recognized that in clinical cases of severe sodium amytal intoxication secretion of urine is apt to be scanty.[6] In the case of pentothal sodium, it has been reported that when

From the Pharmacological Laboratory of the University of Virginia.

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1. Epstein, E.: Influence of Hypnotics and Other Drugs on Thyroxine Diuresis, Arch. f. exper. Path. u. Pharmakol. **142**:214-235, 1929; cited by Lundy, J. S., and Osterberg, A. E.: Review of the Literature on the Derivatives of Barbituric Acid, Proc. Staff Meet., Mayo Clin. **4**:385-416 (Dec. 18) 1929.

2. Epstein, E.: Diuresis After Oral and Intravenous Administration of Liquid and Changes Produced by Hypnotics, Arch. f. exper. Path. u. Pharmakol. **142**: 236-247, 1929; cited by Lundy, J. S., and Osterberg, A. E.: Review of the Literature on the Derivatives of Barbituric Acid, Proc. Staff Meet., Mayo Clin. **4**:385-416 (Dec. 18) 1929.

3. Ogden, E.: Inhibition of Water Diuresis by Amytal, Proc. Soc. Exper. Biol. & Med. **27**:506-507 (March) 1930.

4. Walton, R. P.: Effect on Kidney Function of Ether, Ethylene, Ethylene and Sodium Isoamyl-Ethyl Barbiturate (Amytal), and Ethylene and Tribromethyl Alcohol (Avertin), J. Pharmacol. & Exper. Therap. **47**:141-149 (Feb.) 1933.

5. Gouax, J. L.; Cordill, S. C., and Eaton, A. C.: Influence of Sodium Amytal upon Blood and Urine Urea, J. Lab. & Clin. Med. **22**:704-707 (April) 1937.

6. Emge, L. A., and Hoffman, P. E.: Studies on Urinary Excretion in Women Following Administration of Sodium Amytal, Anesth. & Analg. **10**:88-90 (March-April) 1931.

the drug was used as an anesthetic in urologic practice, no change in urinary secretion or in the concentration of blood urea occurred.[7]

In this paper the influence of the ultra-short-acting thiobarbiturate pentothal sodium [8] on renal activity has been investigated under a variety of experimental conditions in an attempt to elucidate the mechanism of barbiturate antidiuresis. The experiments described here have been grouped as follows:

1. Effect of pentothal sodium on urine output
2. Antagonism of the demonstrated antidiuretic effect of pentothal sodium by various diuretics
3. Effect of corticosterone acetate and adrenal cortex extract on pentothal sodium antidiuresis
4. Effect of epinephrine on pentothal sodium antidiuresis
5. Effect of solution of posterior pituitary on pentothal sodium antidiuresis
6. Effect of hypophysectomy on pentothal sodium antidiuresis

MATERIAL AND METHOD

Male white rats weighing between 160 and 240 Gm. each were employed. All animals fasted for twelve hours before the start of a metabolic period, although they were allowed free access to water during this time. At the end of the preliminary twelve hour fasting period the animals were weighed, given 10 per cent of their body weight of 0.2 per cent sodium chloride solution (warmed to body temperature) by intraperitoneal injection and placed in individual metabolism cages. Urine was collected in 25 cc. graduated cylinders, and the volume recorded at thirty minute intervals during a metabolic period of twelve hours. To insure that no residual urine remained in the bladder, after each interval the bladder was palpated; if urine was present, the fluid was expressed by gentle pressure. In unanesthetized animals this procedure was rarely necessary, but in anesthetized animals with muscular atony it was invariably carefully performed.

All animals to which pentothal sodium was administered were given the calculated dose by intraperitoneal injection at the end of the second hour after fluid was administered. The anesthetic dose for pentothal sodium in these animals, when given by intraperitoneal injection following administration of sodium chloride solution, was found to be 6 mg. per hundred grams of body weight (0.25 cc. of a 2.4 per cent solution). Recovery from this dose was practically complete within six hours, and in several hundred experiments no fatalities resulted. Pratt and associates [9] have given the anesthetic dose of sodium pentothal by intraperitoneal

7. Tovell, R. M., and Thompson, G. J.: Pentothal-Sodium Anesthesia in Urologic Practice, J. Urol. **36**:81-87 (July) 1936.

8. The pentothal sodium was furnished by Dr. J. F. Biehn, of the Abbott Laboratories.

9. Pratt, T. W.; Tatum, A. L.; Hathaway, H. R., and Waters, R. M.: Sodium Ethyl (1-Methyl Butyl) Thiobarbiturate: Preliminary Experimental and Clinical Study, Am. J. Surg. **31**:464-466 (March) 1936.

injection as 80 mg. per kilogram of body weight; recovery from this dose took place in six to twelve hours.

Other drugs were employed under special conditions, which will be individually described. These drugs were so administered that they exerted their optimal characteristic action coincident with the antidiuresis produced by the injection of pentothal sodium.

RESULTS

Control Diuretic Curve.—A control diuretic response was established by administering standard water loads to a large series of rats under the controlled conditions just outlined (table 1 *A*). The diuretic

TABLE 1.—*Effect of Various Doses of Pentothal Sodium on the Urine Output of Rats After Injection of Two-Tenths per Cent Solution of Sodium Chloride* *

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	24	2.4	3.5	4.9	5.5	6.0	6.5	7.0	7.5	7.8	8.3	8.6	8.9	9.3	9.5
B (2 mg. of pentothal sodium /100 Gm. of body weight)	12	1.4	1.8	3.3	4.7	5.6	8.3	6.5	7.0	7.5	7.9	8.2	8.5	8.9	9.0
C (4 mg. of pentothal sodium /100 Gm. of body weight)	12	1.9	1.9	2.4	4.8	5.5	6.1	6.7	7.1	7.6	8.0	8.3	8.5	8.8	9.0
D (6 mg. of pentothal sodium /100 Gm. of body weight)	29	2.1	2.3	2.8	3.2	3.6	4.0	4.6	5.2	6.1	6.5	7.2	7.7	8.0	8.3

* At the beginning of the experiment 10 cc. of saline solution per hundred grams of body weight was injected. When pentothal sodium was used, it was injected at the end of two hours in all experiments.

response to injected fluid under these conditions followed the expected curve (fig. 1), which was easily reproducible in different animals at various times.

Average figures only are given in all tables, beginning with the urine output at the end of two hours. Half hourly readings are recorded until the four and a half hour reading, since these constitute the most significant portion of the curve of diuresis; thereafter, only hourly figures are given in the tables. The graphs represent the best smooth curves which could be drawn through the experimentally determined points.

Effect of the Injection of Pentothal Sodium on Urine Output.—Two hours after intraperitoneal injection of sodium chloride solution into several series of rats various doses of pentothal sodium were admin-

istered. When the dose was 2 mg. per hundred grams of body weight the animals became drowsy and disinclined to spontaneous movement, but no anesthesia occurred, and save for a slight diminution in urine flow immediately following the injection, no difference in the diuretic response as compared to that of the control animals was observed (table 1 *B*). When the dose of pentothal sodium was increased to 4 mg. per hundred grams, the degree of hypnosis was more profound and approached light

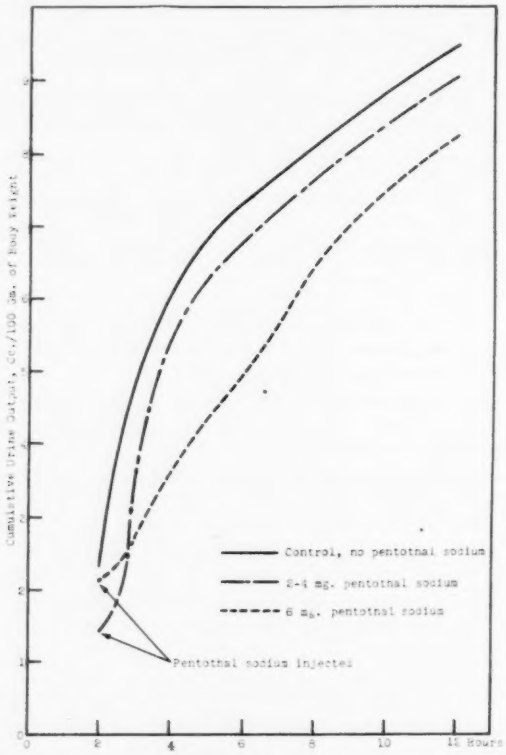

Fig. 1.—Effect of injected pentothal sodium on the urine output of white rats.

anesthesia in about half the animals. The temporary diminution in urine output immediately following injection was somewhat more marked than in the previous series (table 1 *C*; fig. 1).

When the dose was increased to 6 mg. per hundred grams, however, deep anesthesia supervened and lasted for approximately four hours. During this time urine output was markedly decreased, but as the animals recovered consciousness and voluntary movement, the rate of urine flow

once more approached the normal, although the total volume of urine excreted during the twelve hour metabolic period still remained below the control level (table 1 *D*; fig. 1). It should be emphasized here that only fully anesthetic doses of pentothal sodium produced any lasting or significant reduction in the rate and the volume of urine output of rats.

Influence of Sodium Chloride Solution and Urea on Pentothal Sodium Antidiuresis.—Two series of animals were given preliminary priming doses of 10 cc. of 0.9 per cent sodium chloride solution per hundred grams of body weight sixteen hours and eight hours before the start of a metabolic period. At the start of the experiment another dose of 0.9 per cent sodium chloride solution was injected in place of the standard dose of 0.2 per cent solution, and the animals were then placed in metabolism cages. Into one of the series of animals pentothal sodium (6 mg. per

TABLE 2.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Nine-Tenths per Cent Sodium Chloride Solution* *

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	6	1.8	2.2	3.1	4.2	4.7	5.6	7.3	8.2	8.5	8.8	9.5	9.6	9.7	9.7
B (6 mg. of pentothal sodium /100 Gm. of body weight)	6	2.3	2.3	2.3	2.3	2.6	2.6	3.5	4.8	5.5	6.9	7.2	7.7	8.1	8.6

* Ten cubic centimeters of saline solution per hundred grams of body weight was injected intraperitoneally sixteen hours and eight hours before and at the beginning of an experiment.

hundred grams) was injected at the end of the second hour. The diuretic response of normal animals to 0.9 per cent sodium chloride solution under these conditions was marked (table 2 *A*), but this diuresis was promptly and severely inhibited by the injection of pentothal sodium (table 2 *B*; fig. 2). It is therefore apparent that large amounts either of water (i. e. hypotonic solution, table 1 *D*) or of sodium chloride (table 2 *B*) acting as diuretics were unable to antagonize the antidiuresis due to pentothal sodium.

A number of experiments were also performed with 1 per cent urea in 0.2 per cent sodium chloride solution used in place of 0.9 per cent sodium chloride solution, with essentially similar (negative) results.

Influence of Theophylline with Sodium Acetate and with Calcium Salicylate on Pentothal Sodium Antidiuresis.—Two series of animals were primed with preliminary doses of theophylline with sodium acetate as follows: Twenty-four hours before the start of the experiment each

animal received an intraperitoneal injection of 2 mg. of the drug in solution per hundred grams of body weight. Eight hours and sixteen hours later each animal was given an additional dose of 1 mg. of the drug. On the morning of the metabolism experiment the animals then received intraperitoneal injections of 0.2 per cent sodium chloride solution containing 1 mg. of theophylline with sodium acetate per hundred grams and were placed in the cages as usual. Two hours later one series was given pentothal sodium (6 mg. per hundred grams).

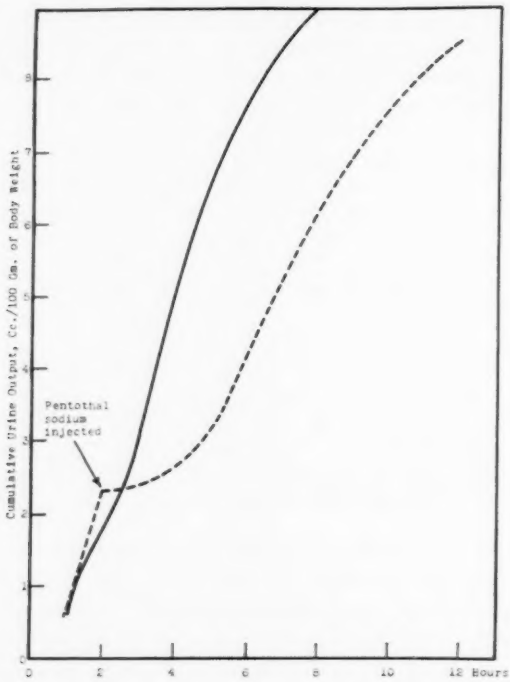

Fig. 2.—Effect of injected pentothal sodium on the urine output of white rats after the administration of 0.9 per cent sodium chloride solution.

The diuretic response of control animals to theophylline with sodium acetate was well marked (table 3 *A*), but this diuretic was nevertheless unable to counteract the pentothal sodium antidiuresis (table 3 *B*). As the anesthetic effect of the barbiturate wore off, however, the diuretic effect of theophylline with sodium acetate became evident; this is well shown by the sudden increase in urine output, corresponding to the emergence of the animals from deep anesthesia (fig. 3).

TABLE 3.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Theophylline with Sodium Acetate* *

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods												
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	12	4.7	6.1	6.5	6.5	6.7	7.0	7.4	7.9	8.1	8.3	8.6	8.7	8.8	8.8
B (6 mg. of pentothal sodium /100 Gm. of body weight)	12	3.3	3.3	3.5	3.9	4.2	4.7	4.9	5.1	5.4	6.2	6.3	6.8	7.0	7.1

* Ten cubic centimeters of 0.2 per cent sodium chloride solution per hundred grams of body weight was injected intraperitoneally at the beginning of the experiment. For the doses of theophylline with sodium acetate, see the text.

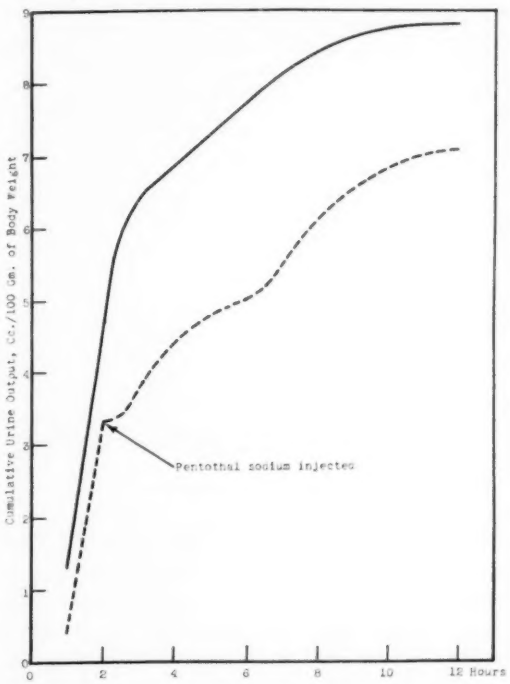

Fig. 3.—Effect of injected pentothal sodium on the urine output of white rats treated with theophylline with sodium acetate.

A number of similar experiments were also performed using theophylline with calcium salicylate (phyllicin) in various doses, but antagonism to pentothal sodium antidiuresis could not be demonstrated.

Influence of Mercurial Diuretics on Pentothal Sodium Antidiuresis.—Eight hours before the start of the experiment two series of animals were given a priming dose of 0.75 mg. of mercupurin per hundred grams of

TABLE 4.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Mercupurin* *

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods												
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	17	2.5	4.4	5.7	5.9	6.2	6.3	6.9	7.4	7.7	8.0	8.3	8.4	8.5	8.7
B (6 mg. of pentothal sodium /100 Gm. of body weight)	14	3.4	3.7	4.4	5.0	5.6	5.8	6.5	7.1	7.4	7.6	7.9	8.2	8.4	8.6

* Ten cubic centimeters of 0.2 per cent sodium chloride solution per hundred grams of body weight was given intraperitoneally at the beginning of the experiment. For the doses of mercupurin, see the text.

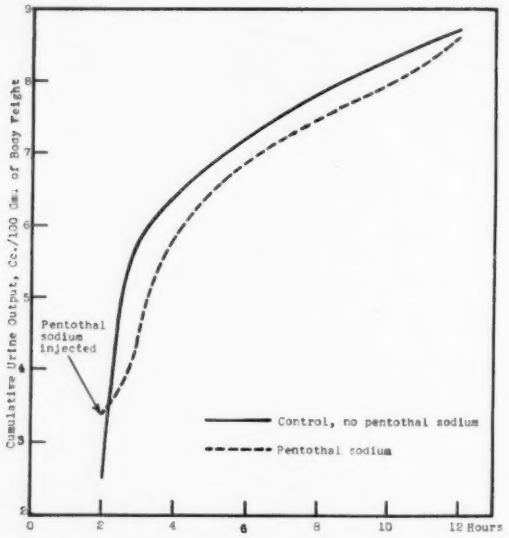

Fig. 4.—Effect of injected pentothal sodium on the urine output of white rats treated with mercupurin.

body weight. At the start of the experiment itself each animal was given a further dose of 0.75 mg. dissolved in the standard 10 cc. of 0.2 per cent sodium chloride solution. One series was given 6 mg. pentothal sodium per hundred grams two hours later.

Copious diuresis was induced in control animals by administration of mercupurin (table 4 *A*). In contrast to the completely negative effect of water, sodium chloride, urea and theophylline with sodium acetate and with calcium salicylate, however, mercupurin was at least partially effective in overcoming pentothal sodium antidiuresis (table 4 *B*). Thus, immediately after the injection of the barbiturate the usual temporary

inhibition of urine flow was observed, but this lasted only a short time, the urine flow rising within ninety minutes almost to the normal rate and level.

Comparable experiments were attempted using salyrgan, but the severe pain which the animals seemed to experience on injection of the drug forced their abandonment.

Influence of Desoxycorticosterone Acetate and Adrenal Cortex Extract on Pentothal Sodium Antidiuresis.—The action of a mercurial diuretic having its site of action on the renal tubular epithelium [10] in overcoming in part pentothal sodium antidiuresis suggested the use of another agent having the same site of action, the adrenal cortex extract.[11] The

TABLE 5.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Desoxycorticosterone Acetate* *

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	10	2.5	3.6	...	5.3	...	5.9	6.6	7.0	7.4	7.9	8.3	8.5	...	8.8
B (6 mg. of pentothal sodium /100 Gm. of body weight)	10	2.7	3.2	...	3.6	...	3.7	4.0	4.8	5.9	6.7	7.1	7.5	...	8.3

* Ten cubic centimeters of 0.2 per cent sodium chloride solution per hundred grams of body weight was injected intraperitoneally at the beginning of the experiment. All animals were given 3 mg. of desoxycorticosterone acetate in oil per hundred grams of body weight subcutaneously four hours before the start of the experiment.

effects of desoxycorticosterone acetate [12] and of adrenal cortex extract on pentothal sodium oliguria were therefore determined.

Four hours before the start of an experiment a number of animals were given subcutaneous injections of 3 mg. of desoxycorticosterone acetate in oil per hundred grams of body weight. Hypotonic solution of sodium chloride was then administered in the usual fashion, and at the

10. (*a*) Blumgart, H. L., and others: Action of Diuretic Drugs: Action of Diuretics in Normal Persons, Arch. Int. Med. **54**:40-81 (July) 1934. (*b*) Walker, A. M.; Schmidt, C. F.; Elsom, K. A., and Johnston, C. G.: Renal Blood Flow of Unanesthetized Rabbits and Dogs in Diuresis and Antidiuresis, Am. J. Physiol. **118**:95-110 (Jan.) 1937.

11. Silvette, H., and Britton, S. W.: Renal Function in the Opossum and the Mechanism of Cortico-Adrenal and Post-Pituitary Action, Am. J. Physiol. **123**: 630-639 (Sept.) 1938.

12. This compound was furnished by Dr. Ernst Oppenheimer, of Ciba Pharmaceutical Products, Inc.

end of two hours pentothal sodium (6 mg. per hundred grams) was injected into half the animals. Desoxycorticosterone acetate alone was without influence on the normal diuretic response of rats to 0.2 per cent sodium chloride solution (table 5 *A*) and also without effect on the course of pentothal sodium antidiuresis (table 5 *B*).

A supply of adrenal cortex extract made by a modified Swingle-Pfiffner method [13] was furnished by Dr. S. W. Britton, but when tested in the manner just described it was also found to be without effect either on control rats or on animals given pentothal sodium. It had previously been observed that adrenal cortex extract showed no diuretic effect when the rate of urine formation was already high.[11]

Influence of Epinephrine Base in Oil on Pentothal Sodium Antidiuresis.—Two series of animals were given intraperitoneal injections

TABLE 6.—*Effect of Pentothal Sodium on the Urine Output of Rats After Injection of Epinephrine Base in Oil* *

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods												
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	10	3.1	4.1	4.8	5.1	5.4	5.5	5.7	6.0	6.4	6.7	6.8	6.8	6.9	6.9
B (6 mg. of pentothal sodium /100 Gm. of body weight)	10	3.5	3.8	4.7	5.1	5.2	5.5	5.7	5.8	6.1	6.3	6.4	6.4	6.8	7.0

* Ten cubic centimeters of 0.2 per cent sodium chloride solution per hundred grams of body weight was injected intraperitoneally at the beginning of the experiment. For the dose of epinephrine base in oil, see the text.

of 0.2 per cent sodium chloride solution in the usual way and also simultaneous subcutaneous injections of epinephrine base in oil (0.5 mg. per hundred grams). Two hours later one series was given injections of pentothal sodium (6 mg. per hundred grams).

The administration of epinephrine to control animals resulted in a considerable increase in diuretic response during the early part of the metabolic period, which, however, was not sustained throughout the entire twelve hour period (table 6 *A*). The diuretic response of the animals given pentothal sodium was nevertheless identical with that of the controls (table 6 *B*; fig. 5), thus indicating antagonism of pentothal sodium antidiuresis by epinephrine.

13. Ehrenstein, M., and Britton, S. W.: The Purification of Adrenal Extracts and Isolation of an Activator of Male Sex Hormones, Am. J. Physiol. **120**:213-221 (Oct.) 1937.

Influence of Solution of Posterior Pituitary on Pentothal Sodium Antidiuresis.—The effect of this substance on the course of pentothal sodium antidiuresis was determined in a number of experiments. Two series of animals were given intraperitoneal injections of 1.5 units of posterior pituitary extract (0.15 cc. of solution of posterior pituitary U. S. P.) per hundred grams of body weight thirty minutes before the routine injection of 0.2 per cent sodium chloride solution. The antidiuretic effect of the posterior pituitary solution was apparent by the end of the second hour, at which time one of the series of animals received an injection of pentothal sodium (6 mg. per hundred grams). Simple

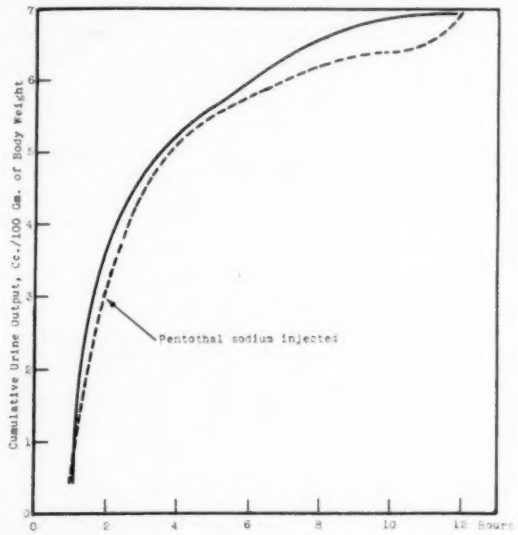

Fig. 5.—Effect of injected pentothal sodium on the urine output of white rats treated with epinephrine base in oil.

pituitary antidiuresis in the control animals lasted about eight hours, after which escape from pituitary inhibition occurred and a rapid rate of urine formation followed (table 7 *A*). Injection of pentothal sodium had an additive antidiuretic effect; inhibition of urine formation in animals receiving both posterior pituitary extract and pentothal sodium was greater and more prolonged than in those animals receiving posterior pituitary solution alone (table 7 *B*; fig. 6).

In two other series of animals the same dose of posterior pituitary solution was injected thirty minutes after the injection of pentothal

sodium rather than two and a half hours before, as in the previous experiments. But whereas subsequent injection of the latter drug merely reenforced the original pituitary antidiuresis, when pentothal sodium oliguria was induced first the subsequent injection of posterior pituitary solution had no antidiuretic effect (table 7 *D*) or even a slightly diuretic one compared with the control series (table 7 *C*; fig. 7). These results are in agreement with the well known observation that the injection of posterior pituitary solution into anesthetized animals is followed by diuresis rather than by inhibition of urine secretion.[14]

TABLE 7.—*Effect of Pentothal Sodium on Antidiuresis Caused by Solution of Posterior Pituitary* *

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods												
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
I. Solution of Posterior Pituitary Injected 30 Minutes Before Start of Experiment (—0.5 Hr.)															
A (no pentothal sodium) (control series)	6	0.8	1.1	1.3	1.4	1.5	1.7	1.7	1.8	2.0	2.3	2.7	3.3	4.2	4.3
B (6 mg. of pentothal sodium /100 Gm. of body weight)	6	0.7	0.8	0.8	0.8	0.8	0.9	0.9	1.0	1.1	1.1	1.2	1.4	1.5	1.8
II. Solution of Posterior Pituitary Injected 30 Minutes after Injection of Pentothal Sodium (2.5 Hr.)															
C (no pentothal sodium) (control series)	18	1.7	2.2	2.7	3.2	3.5	3.9	3.9	4.4	4.4	4.5	4.6	4.7	4.9	5.0
D (6 mg. of pentothal sodium /100 Gm. of body weight)	18	1.7	1.8	2.3	3.2	3.9	4.2	4.7	4.9	5.1	5.2	5.3	5.3	5.4	5.5

* All animals received 10 cc. of 0.2 per cent sodium chloride solution per hundred grams of body weight at the beginning of the experiment. For details of treatment with solution of posterior pituitary, see the text.

Influence of Hypophysectomy on Pentothal Sodium Antidiuresis.—A number of male rats were completely hypophysectomized by Dr. E. L. Corey and were maintained after the operation for three to four weeks until the initial polyuria was succeeded by an essentially normal water intake and urine output.[15] At this time extensive atrophy of the gonads

14. Richards, A. N., and Plant, O. H.: Action of Minute Doses of Adrenalin and Pituitrin on Kidney, Am. J. Physiol. **59**:191-202 (Feb.) 1922. Nelson, E. E.: Diuretic Effect of Posterior Pituitary Extract in Anesthetized Animals, J. Pharmacol. & Exper. Therap. **52**:184-195 (Oct.) 1934.

15. Corey, E. L., and Britton, S. W.: Course of Diabetes Insipidus Following Hypophysectomy in the Rat, Proc. Soc. Exper. Biol. & Med. **46**:678-679 (April) 1941.

was evident, indicating complete removal of the pituitary. Such hypophysectomized animals were found to be extremely sensitive to pentothal sodium. Doses of 6 mg. per hundred grams, which were merely anesthetic in normal rats, were invariably fatal to hypophysectomized animals.

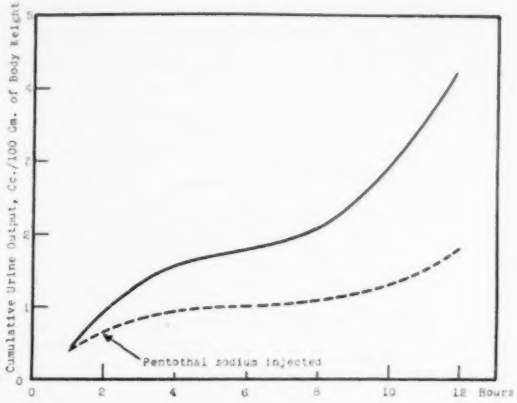

Fig. 6.—Effect of injected pentothal sodium on urine output of white rats after the administration of solution of posterior pituitary.

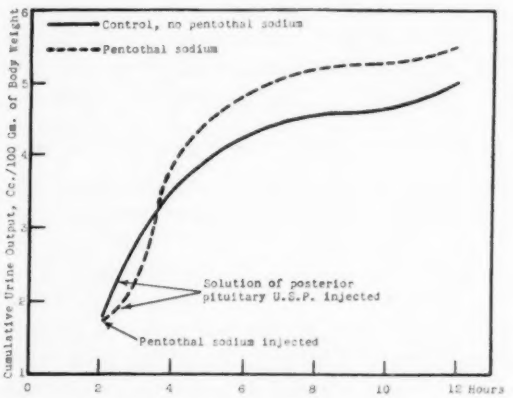

Fig. 7.—Effect of an injection of pentothal sodium followed by administration of solution of posterior pituitary on the urine output of white rats.

A dose of 4 mg. of pentothal sodium per hundred grams was found to be well sustained and fully anesthetic and was therefore employed in place of the standard dose of 6 mg. used in animals which had not been operated on.

TABLE 8.—*Effect of Pentothal Sodium on the Urine Output of Hypophysectomized Rats After Injection of Two-Tenths per Cent Sodium Chloride Solution* *

Series	No. of Rats in Series	Cumulative Urine Output in Cc./100 Gm. of Body Weight at End of Given Periods													
		2.0 Hr.	2.5 Hr.	3.0 Hr.	3.5 Hr.	4.0 Hr.	4.5 Hr.	5.5 Hr.	6.5 Hr.	7.5 Hr.	8.5 Hr.	9.5 Hr.	10.5 Hr.	11.5 Hr.	12.0 Hr.
A (no pentothal sodium) (control series)	6	1.1	1.2	1.4	1.7	1.8	2.3	2.5	3.1	3.6	3.8	4.2	4.6	4.7	5.1
B (4 mg. of pentothal sodium /100 Gm. of body weight)	6	0.7	0.9	1.0	1.1	1.4	1.6	1.7	2.0	2.2	2.5	2.6	2.7	2.7	2.7

* Ten cubic centimeters of saline solution per hundred grams of body weight was injected at the beginning of the experiment.

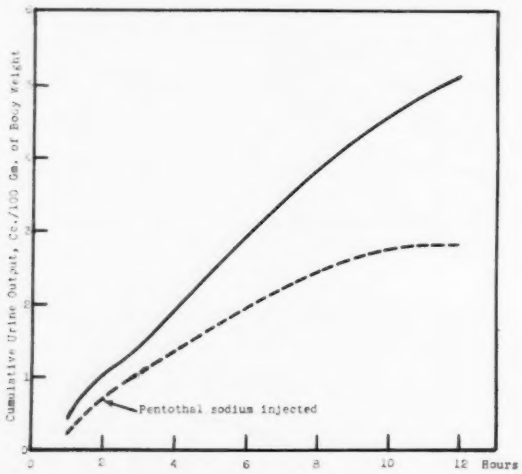

Fig. 8.—Effect of injected pentothal sodium on the urine output of long-surviving hypophysectomized white rats given 0.2 per cent sodium chloride solution.

A series of 6 long-surviving, completely hypophysectomized rats in good condition was given intraperitoneal injections of 10 cc. of 0.2 per cent sodium chloride solution per hundred grams, and a control diuretic response was established (table 8 *A*). Three days later the same animals were again tested, this time with an additional injection of 4 mg. of pentothal sodium two hours after the initial injection of fluid. Pentothal sodium antidiuresis was found to be as marked in these hypophysectomized rats as in normal animals which had not been operated on (table 8 *B*; fig. 8).

Many other hypophysectomized rats were tested individually for diuretic response, some with and some without subsequent injection of pentothal sodium. In all cases the animals receiving injections of the drug showed a definite inhibition of secretion of urine.

COMMENT

It may be assumed for purposes of discussion that the principal influences leading to antidiuresis are the antidiuretic hormone of the posterior lobe of the hypophysis, renal tubular reabsorption of water and lowered blood pressure in the glomerulus, either primary or secondary as a reflection of general hypotension.

The mechanism by which barbiturates inhibit the secretion of urine has been described in a recent text book as "probably a central one on the hypophyseal-pituitary [sic] system."[16] De Bodo and Bloch in a preliminary report cited evidence which inferentially supports this view.[17] In their experiments phenobarbital in small nonanesthetic doses decreased the excretion of water approximately 50 per cent in normal dogs, but in dogs with diabetes insipidus (produced by the destruction of the entire neurohypophysis) this same dose had no effect on excretion of water. If animals so treated indeed do not show barbiturate antidiuresis, the conclusion is implicit that barbiturates, while depressing all other nervous centers, stimulate the hypophysis (or the hypothalamicohypophyseal system) to secrete its antidiuretic hormone which by increasing renal tubular reabsorption of water results in decreased urine output. Any such selective stimulation seems highly improbable, especially since the hypothalamus appears to be one of the regions of greatest susceptibility to barbiturate depression,[18] and there is no evidence of it from the results of my experiments on hypophysectomized rats. In these long-surviving, completely hypophysectomized animals, which had passed the polyuric stage, the injection of pentothal sodium had the same antidiuretic effect as in normal animals. This indicates that the hypothalamicohypophyseal system is not involved in the production of pentothal sodium oliguria in rats.

On the other hand, the site of pentothal sodium antidiuresis does not seem to be the renal tubular epithelium either, since this urinary inhibition is not antagonized by diuretics (by theophylline with sodium acetate or with calcium salicylate or by mercupurin) or by adrenal cortex extract which acts to inhibit renal reabsorption of water by the renal tubules. (The conclusions of Walker and associates[10b] are accepted, that xanthine diuresis is not accompanied by significant changes in renal blood flow or glomerular filtration but results from decreased tubular reabsorption of

16. Goodman, L., and Gilman, A.: Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 134.

17. De Bodo, R. C., and Bloch, H. I.: The Effect of Narcotics on Diuresis, J. Pharmacol. & Exper. Therap. **72**:4-5 (May) 1941.

18. Marshall, E. K., Jr.; Walzyl, E. M., and LeMessurier, D. H.: Picrotoxin as a Respiratory Stimulant, J. Pharmacol. & Exper. Therap. **60**:472-486 (Aug.) 1937.

fluid.) Mercurial diuretics,[19] theophylline with sodium acetate and with calcium salicylate[20] and desoxycorticosterone acetate[21] all antagonize pituitary antidiuresis, the site of which is agreed to be the tubular epithelium.[22] The fact that these agents do not also antagonize pentothal sodium antidiuresis renders it highly likely that the origin of this urinary inhibition does not lie in the renal tubules.

Diuretics which exert their effects by the osmotic retention of water within the renal unit (as sodium chloride and urea) are ineffective in overcoming pentothal sodium antidiuresis.

By the process of exclusion both of posterior pituitary and of renal factors in the production of pentothal sodium antidiuresis, the effect of injection of pentothal sodium in producing oliguria must therefore be due to alteration in glomerular blood pressure, either primarily or secondarily induced. Experiments on the effect of epinephrine in antagonizing this antidiuresis offer confirmation of this conclusion.

It is well understood that barbiturates, like other anesthetics, may affect urine secretion indirectly through the circulation. The hypotension which characterizes an overdose of a barbiturate results in oliguria or even anuria.[23] Rapid intravenous injection of pentothal sodium results in a sudden fall in blood pressure, which, however, soon returns to normal.[24] When the drug is intraperitoneally injected, as in these experiments, a fall in blood pressure occurs during the antidiuretic phase.[25] This lowered blood pressure apparently results from vasodilatation due to the depressant effect of barbiturates on smooth muscle.[26] Particularly in the case of pentothal sodium this leads to congestion, stasis and hemorrhage in the kidneys,[27] which would result in oliguria even

19. Raab, W.: Effect of Pituitrin on Water Metabolism, Water Content of Blood and on Diuresis, Wien. Arch. f. inn. Med. **17**:471-512 (June) 1929.

20. Goodman and Gilman,[16] p. 649.

21. Corey, E. L., and Britton, S. W.: The Antagonistic Action of Desoxycorticosterone and Post-Pituitary Extract on Chloride and Water Balance, Am. J. Physiol. **133**:511-519 (July) 1941.

22. Silvette, H.: The Influence of Post-Pituitary Extract on the Excretion of Water and Chlorides by the Renal Tubules, Am. J. Physiol. **128**:747-753 (March) 1940.

23. Goodman and Gilman,[16] p. 134.

24. Gruber, C. M.: Effect of Anesthetic Doses of Sodium Thio-Pentobarbital, Sodium Thio-Ethamyl and Pentothal Sodium upon Respiratory, Heart, and Blood Pressure Changes in Experimental Animals, J. Pharmacol. & Exper. Therap. **60**: 143-173 (June) 1937.

25. Corey, E. L., and Silvette, H.: Unpublished data.

26. Gruber, C. M., and Gruber, C. M., Jr.: Segments of Excised Small Intestine as Affected by the Sodium Salts of Thioamyl, Thiopentobarbital, Pentobarbital and Evipal, J. Pharmacol. & Exper. Therap. **66**:16-17 (May) 1939.

27. Gruhzit, O. M.; Dox, A. W.; Rowe, L. W., and Dodd, M. C.: Pharmacologic Study of Certain Thiobarbiturates, J. Pharmacol. & Exper. Therap. **60**: 125-142 (June) 1937.

without the appearance of generalized hypotension. That the oliguria in the experimental animals was caused by local renal, or later by more generalized, hypotension is suggested by the fact that the urine flow could be maintained at control levels in these animals only by the injection of epinephrine in suitable concentration. In minute amounts epinephrine may cause constriction of the efferent renal arterioles before systemic vasoconstriction is evident,[28] thus leading to increased effective filtration pressure within the capillary tufts, even though no increase in systemic blood pressure occurs. This would seem to be the mechanism by which pentothal sodium antidiuresis was immediately overcome, followed by more generalized vasoconstriction as the concentration of injected epinephrine increased.

In connection with the antagonistic effect of epinephrine in overcoming pentothal antidiuresis, it is interesting to note that Gruber and associates [29] found that only epinephrine restored the normal rhythm in animals' hearts rendered arrhythmic by pentothal sodium. Experiments are now under way designed to correlate the course of pentothal sodium antidiuresis with the presence of pentothal sodium cardiac arrhythmia.

The results of the experiments herein described lead to the conclusion that pentothal sodium antidiuresis results from hypotension, either renal or general, brought about by the thiobarbiturate. Furthermore, the results also indicate that pentothal sodium does not exert any direct action either on the renal unit or on the hypothalamicohypophyseal system in producing antidiuresis in rats.

SUMMARY

The injection of anesthetic doses of pentothal sodium (6 mg. per hundred grams body weight) into diuretic rats resulted in oliguria during the duration of the anesthesia. Subanesthetic doses (2-4 mg.) had no significant effect on urine output, save for temporary slight antidiuresis immediately following injection.

The course of pentothal sodium antidiuresis was not affected by the administration of diuretics (water, sodium chloride, urea or theophylline with sodium acetate or with calcium salicylate) or desoxycorticosterone acetate. Mercupurin counteracted in part the pentothal sodium oliguria.

28. Hoskins, R. G., and Gunning, R. E. L.: Volume Changes and Venous Discharge in the Kidney, Am. J. Physiol. **43**:304-310 (May) 1917.

29. Gruber, C. M.; Haury, V. G., and Gruber, C. M., Jr.: Cardiac Arrhythmia, Characteristic Effect of Thio-Barbiturates (Pentothal, Thio-Pentobarbital, and Thio-Ethamyl) as Influenced by Changes in Arterial Blood Pressure, J. Pharmacol. & Exper. Therap. **63**:193-213 (June) 1938. Gruber.[24]

Injection of epinephrine in suitable concentration antagonized the antidiuretic effect of pentothal sodium and brought about a diuretic response identical with that of the control animals.

Completely hypophysectomized rats past the polyuric stage showed the same inhibition of water diuresis after injection of pentothal sodium as did animals which had not been operated on.

In animals anesthetized with pentothal sodium the injection of posterior pituitary solution was not followed by antidiuresis but by slight diuresis. Administration of pentothal sodium to rats rendered antidiuretic by injection of posterior pituitary extract resulted in more marked oliguria than that observed after injection of posterior pituitary extract alone.

From these and other considerations the conclusion was reached that pentothal sodium antidiuresis in rats results from hypotension, either renal or general. Furthermore, the results indicate that in the production of pentothal sodium antidiuresis the thiobarbiturate exerted no direct action on the renal unit or on the hypothalamicohypophyseal system.

Box 1353, University of Virginia.

Progress in Internal Medicine

GASTROENTEROLOGY

A REVIEW OF THE LITERATURE FROM JULY 1941 TO JULY 1942

CHESTER M. JONES, M.D.
Physician, Massachusetts General Hospital; Clinical Professor of Medicine, Harvard University
BOSTON

Much of the past year's literature on gastroenterologic subjects consists in confirmation or refutation of previously advanced ideas and observations. Such a state of flux is inevitable in consideration of the fact that experimental observations fundamentally represent a continuous process of addition, with occasional subtraction because of newer evidence. For this reason in any review it is necessary and wise to include much that is not entirely new but which sheds light on current ideas, many of which need modification and some of which need to be stressed again and again in order to establish the importance of fundamental clinical or physiologic principles. As in previous years, I will attempt to present a composite impression of many, but by no means all, of the articles that have appeared during the past year, avoiding as far as possible the inclusion of certain contributions which are merely repetitions of already recorded observations. An attempt has been made to separate the material into two major groups, one dealing with experimental or clinical observations on the functioning of the digestive tract and the other dealing largely with disease entities or with specific symptoms.

GASTROINTESTINAL FUNCTION

Motor.—The relation between the higher levels of the central nervous system and the motor function of the gastrointestinal tract has been appreciated for a long time, but continued search is still indicated for a determination of the actual pathways that are involved and the way in which these pathways function. A study by Hesser, Langworthy and Kolb [1] of gastric activity released from cortical control is pertinent. These authors in experiments on cats recorded graphically definite alterations in gastric tone and motility following ablation of the cerebral motor cortices. Such alterations were demonstrable as greater per-

1. Hesser, F. H.; Langworthy, O. R., and Kolb, L. C.: Experimental Study of Gastric Activity Released from Cortical Control, J. Neurophysiol. **4**:274, 1941.

sistency, consistency and strength of stomach contractions along with increased tone of measured distention of the stomach. These changes were interpreted as evidence of a release from a regulating influence by the motor cortex. A marked stretch reflex with delayed relaxation of the stomach wall after sudden distention was also apparent. Similar modifications were noted in esophageal motility, and on the basis of previous experiments the authors quite properly suggest that the smooth muscle of the stomach and the esophagus is controlled by reflex pathways in the nervous system similar to those which control tone and contraction in the bladder. In this connection it is wise to recall the remarkable observations of Beaumont on St. Martin, with particular reference to motor and vascular changes in the stomach following emotional disturbances. The recent observations by Wolff and Wolf [2] on changes in the vascularization and the motor and secretory activity of the human stomach, as observed in a patient with a gastrostomy, are further confirmation of the intimate connection between the higher nerve centers and the function of the digestive tract. This study by Wolff and Wolf constitutes one of the most important visual demonstrations of such a correlation that has yet been made and provides the basis for a much clearer understanding of various transient or even more permanent changes that are to be encountered as manifestations of disease of the digestive tract in human beings. A somewhat metaphysical study by McGlade [3] may have a remote bearing on the preceding experiments. He studied the relation between the movements of the extremities occurring after the onset of sleep when certain foods were eaten one hour before going to bed. Each foot movement was found to coincide with the sound of the relaxing pyloric sphincter, suggesting evacuation of the stomach, and the author believes that he has secured evidence that the relation between these groups of movements and varied ingestion times not only was predictable in all cases but bore a definite time relation to dreams occurring at the end of the movements.

A type of conditioned reflex involving buccal sensation and alterations in gastric motor activity was studied in dogs by Bulygin,[4] who created chronic fistulas in the fundal and the pyloric part of the stomach and in the duodenum. Irritating substances introduced into the mouth produced

2. Wolff, H. G., and Wolf, S.: Studies on a Subject with a Large Gastric Fistula: Changes in the Function of the Stomach in Association with Varying Emotional States, read at the meeting of the Association of American Physicians, Atlantic City, N. J., May 5, 1942.

3. McGlade, H. B.: The Relationship Between Gastric Motility, Muscular Twitching During Sleep and Dreaming, Am. J. Digest. Dis. **9**:137, 1942.

4. Bulygin, I. A.: Reflex Influence from the Oral Cavity upon the Gastric and Duodenal Movements, J. Physiol. U. S. S. R. **27**:331, 1939; abstracted, Biol. Abstr., Sect. B **16**:3999, 1942.

an increase in gastric and duodenal movements in most instances, whereas water produced little if any change. If, however, water was introduced into a dog's mouth on the day following the experiments with irritating substances, the effect was the same as if an irritating substance had been placed in the mouth and appeared to be evidence of a conditioned reflex. After a certain number of days this reflex disappeared but could be renewed by repeating the experiment. The nervous pathways for the reflex regulation of intestinal pressure were studied in dogs by Youmans, Karstens and Aumann.[5] After determining by recording methods on Thiry fistulas that inhibition of one segment of the intestine could be obtained by distention of another segment, various observations were made after bilateral vagotomy at the level of the lower portion of the esophagus or at the midcervical region or after the splanchnic nerves were cut and the lumbar sympathetic chains were removed. What was called the "intestino-intestinal inhibitory reflex" was abolished by sympathectomy alone but was not noticeably altered by vagotomy. The conclusion was reached that only the sympathetic nervous system contains both afferent and efferent pathways for this particular reflex. The authors maintained that the regulation of intestinal motility by extrinsic nerves consists, in part, of reflex inhibition of the intestine as a result of stimuli arising from excessively strong contractions. One function of this reflex might be that of helping to keep the pressure within the intestine below the level which blocks blood flow through the vessels of the intestinal wall, a point that would have a direct bearing on some of the phenomena observed in intestinal obstruction. Whether sensory afferent pathways are confined to the sympathetic fibers, as has usually been thought to be the case and as is suggested by the foregoing results, is a matter for careful speculation and observation in relation to the phenomenon of pain arising from the digestive tract.

Recognition of the possibility that gastrointestinal motility may be importantly modified by deficiencies in one or more members of the vitamin B complex continues to be encountered in numerous articles, such as those by Mackie [6] and Martin and his collaborators.[7] Changes in the roentgen pattern of the small intestine may occur in a variety of conditions, and it is well known that they may be indicative, at times, of real deficiency disease. Mackie enumerates many of the conditions, such as sprue and steatorrhea, that are associated with a changed pattern

5. Youmans, W. B.; Karstens, A. I., and Aumann, K. W.: Nervous Pathways for the Reflex Regulation of Intestinal Pressure, Am. J. Physiol. **135**:619, 1942.

6. Mackie, T. T.: Vitamin Deficiencies and the Small Intestine, J. A. M. A. **117**:910 (Sept. 13) 1941.

7. Martin, G. J.; Thompson, M. R., and DeCarvajal-Forero, J.: The Influence of Inositol and Other B Complex Factors upon the Motility of the Gastro-Intestinal Tract, Am. J. Digest. Dis. **8**:290, 1941.

and points out what may be a pertinent fact—that exactly the same pattern is presented by the intestine of the newborn infant. Since this "deficiency pattern" of the small bowel noted in early infantile life disappears completely during the child's later development, it would seem that indirect evidence was available that is highly suggestive of a modification of the intrinsic nervous plexus covering intestinal motility. Degeneration of Auerbach's and of Meissner's plexus is known to occur in such a deficiency state as pellagra. By analogy, one may be justified in concluding that reversal of the mucosal pattern supposed to be characteristic of deficiency disease following the administration of vitamin B may be entirely due to the effect of some part of the complex on the intrinsic nerve supply of the intestine. Such a concept would be similar to the known results of thiamine administration on the changes in peripheral nerves encountered in patients with beriberi. Evidence seems to show that the administration of the vitamin B complex in the form of crude liver extract or yeast is much the most effective therapeutic method and indicates that such changes as have been observed may, in part at any rate, depend on some other factor than thiamine, riboflavin or nicotinic acid. Martin, Thompson and DeCarvajal-Forero [7] suggest, on the basis of animal experiments, that inositol and nicotinic acid are the members of the vitamin B complex directly concerned with motor function and that a balance or ratio of nicotinic acid or similar compounds to inositol is the nutritional factor which determines hypomotility or hypermotility. That the changes in gastrointestinal motility associated with a dietary lack of vitamin B_1 are not due to malnutrition alone is indicated in the animal experiments of Gershon-Cohen and his associates.[8] A comparison of the motility of the small bowel in animals on a vitamin B_1–deficient diet and in a similar group under starvation conditions indicated that starvation alone produced minimal changes in the tonicity of the entire digestive tract.

Some experiments have been attempted to determine the effect of avitaminosis A on gastric emptying time, and in half of the experimental animals used by Herrin [9] the final emptying time of the stomach was strikingly increased under deficiency conditions. The results were variable, however, and it would seem that lack of vitamin A intake had little important influence directly on the motor activity of the stomach, except possibly as a reflection of a general nutritional disturbance. It is also of interest to note that in Herrin's experiment the presence of avitaminosis A had no appreciable effect on the acid secretion of the stomach.

8. Gershon-Cohen, J.; Shay, H., and Fels, S. S.: B_1 Avitaminosis: Roentgenologic Studies of Gastro-Intestinal Tract in Rats on Vitamin B_1 Deficiency Diets, Am. J. Roentgenol. **46**:876, 1941.

9. Herrin, R. C.: Gastric Emptying Time and Acidity in Avitaminosis A in Dogs, Am. J. Digest. Dis. **7**:164, 1940.

By the use of balloons and the kymograph hypermotility of the human stomach was demonstrated by Hamilton and Curtis [10] during the clinical appearance of "gas pains," late postoperative nausea, "pylorospasm" secondary to ulcer, biliary colic, etc. During the clinical manifestations of these varying conditions gastric hypermotility occurred simultaneously with varying degrees of clinical distress. Moreover, the patients ceased to complain of pain or discomfort when the stomach was quiescent. Whether hypomotility was spontaneous or induced by atropine made no apparent difference. Such observations help to clarify the mechanism underlying symptoms common to various disease conditions and indicate the form of therapy needed. Further observations on the phenomena occurring during nausea are contributed by Ingelfinger and Moss.[11] Observations were made on 5 normal volunteers and on 15 patients, 5 of whom had organic disease of varying types. Kymographic records of duodenal activity were obtained after labyrinthine excitation or after the administration of morphine sulfate. By one of these two methods nausea was produced in most instances and was associated with a generalized contraction of the descending duodenum, which frequently resulted in the expulsion of balloons backward into the stomach, without, however, any demonstrable evidence of reverse peristalsis. The authors believe that duodenal spasm is a frequent concomitant of nausea and results in a pushing of the duodenal contents into the stomach by reversing the intestinal gradient. Necessarily, they point out, pylorospasm during nausea would seem to be impossible.

A prolonged initial depression of gastric motility and tone following the use of insulin is reported by Necheles, Olson and Morris [12]; this depression was coincidental with hypoglycemia. As the blood sugar rose to medium and slightly low values, the typical insulin hypermotility appeared. The authors explain this initial hypomotility on the basis of an increased epinephrine response to hypoglycemia and suggest, therefore, that the clinical use of insulin in cases of anorexia should be limited to the administration of rather small doses in order to avoid marked hypoglycemia.

Brown, Pendergrass and Burdick [13] compare the motor activity of the gastrointestinal tract in 24 patients with hyperthyroidism and 14 normal

10. Hamilton, F. E., and Curtis, G. M.: Clinical Indications for Inducing Gastric Hypomotility, J. A. M. A. **117**:2228 (Dec. 27) 1941. Hamilton, F. E.: The Clinical Significance of Human Gastric Motility, Ann. Surg. **114**:153, 1941.

11. Ingelfinger, F. J., and Moss, R. E.: The Activity of the Descending Duodenum During Nausea, Am. J. Physiol. **136**:561, 1942.

12. Necheles, H.; Olson, W. H., and Morris, R.: Depression of Gastric Motility by Insulin, Am. J. Digest. Dis. **8**:270, 1941.

13. Brown, R. B.; Pendergrass, E. P., and Burdick, E. D.: The Gastro-Intestinal Tract in Hyperthyroidism, Surg., Gynec. & Obst. **73**:766, 1941.

persons and conclude that the following gastrointestinal changes are characteristic of hyperthyroidism: (1) an increased incidence of achlorhydria; (2) an increased prominence of gastric rugae; (3) an increase in the rapidity with which the stomach starts to empty; (4) a delay in gastric emptying following the initial increase; (5) increased tone of the small intestine with an abnormal pattern; (6) increased motility of the small intestine, and (7) a similar increase in tone and motility of the large intestine. A previously unpublished observation by Castleton [14] on the effect of artificial hyperthyroidism on the rate of rhythmic contractions both of intact and of excised small intestine of rabbits confirms the foregoing observations. This author believes it possible that the increase in the rate of rhythmic contractions is associated with an increase in the irritability of the bowel and that these changes may have something to do with the production of the diarrhea that is frequently noted in the thyrotoxic state. That the translation of the results of such animal experiments from one species to another or to human beings may not be appropriate is indicated in the experiments of Oppenheimer and Glyer,[15] who made observations on the motor activity of exteriorized intestinal loops in dogs. These loops included areas from high up in the jejunum to just above the ileocecal valve. The administration of thyroid in doses sufficient to elevate the basal metabolic rate 50 per cent did not alter the rate of contraction except in a segment just above the ileocecal valve. That increases in metabolic rate alone are insufficient to account for such motor changes is indicated by the fact that preparations of alpha-1,2,4-dinitrophenol given in doses sufficient to elevate the rate over 200 per cent did not increase the rate of contraction in the exteriorized loops. That some other mechanism may be involved in the diarrhea of hyperthyroidism is suggested, at any rate, by the report of Bartels.[16] In a group of patients suffering from diarrhea in association with hyperthyroidism and in whom the usual measures to control hypermotility of the bowel were ineffective, the administration of lipocaic restored normal intestinal function in the course of a short time. In 1 instance the return of hyperthyroidism was again associated with diarrhea, which was once more controlled by the use of lipocaic, suggesting the possible effect of lipocaic in supplementing the internal secretion of the alpha cells of the depleted pancreas.

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14. Castleton, K. B.: The Rate of Rhythmic Contraction of the Small Bowel of Rabbits as Influenced by Experimentally Produced Hyperthyroidism, Am. J. Digest. Dis. **8**:473, 1941.

15. Oppenheimer, M. J., and Glyer, N. M.: The Effect of Elevated Metabolism on Rate of Intestinal Contractions, Am. J. Digest. Dis. **8**:471, 1941.

16. Bartels, E. C.: Lipocaic in Treatment of Diarrhea of Hyperthyroidism: Preliminary Report, West. J. Surg. **49**:439, 1941.

Larson [17] studied the effect of preparations of posterior pituitary on the motility of the large intestine in unanesthesized dogs. Giving solutions of posterior pituitary or pitocin intravenously resulted in a decrease in tone and motility of the upper and the lower portion of the large bowel. Pitressin was without effect. Subcutaneous or intramuscular injections of varied doses of solution of posterior pituitary or of pitressin usually caused only an increase in motility in the upper portion of the large bowel. Subcutaneous injection of pitocin had little or no effect on tone or motility.

The effect on motility of the exclusion of bile from the intestinal tract has been studied by Ackerman, Curl and Crandall.[18] In dogs with bile fistulas there was an increase in the rate of gastric evacuation and of the entrance of barium sulfate into the large intestine following a mixed meal. After a fat meal there was a slower gastric emptying time than in normal animals, which was increased by the administration of bile salts with the fat meal. These authors state that the suggestion that bile salts are an important factor in the regulation of the motility of the small intestine is not supported by their observations. It is possible that such observations indicate the need for a search for some other factor than the absence of bile salts as the one responsible for the rapid intestinal rate so frequently noted in patients with obstructive jaundice.

Studies made by Quigley and Meschan [19] with the tandem balloon method demonstrated that fatty acids or soaps introduced into the proximal portion of the intestine of fasting dogs inhibited the motility of the pyloric antrum sphincter and the duodenal bulb in a manner qualitatively similar to that in which natural fats acted. Such retardation of gastric evacuation apparently resulted from decreased antral peristalsis and occurred in spite of a relaxed sphincter. The evidence indicated that if natural fats were administered, they initiated the reaction and the products of digestion continued the influence. Analagous experiments are reported by Tidwell and Cameron,[20] the results of which indicate that the gastric inhibitory response to fat varies with its chemical composition, a finding similar to that noted by the preceding authors. The statement is made that there is a striking parallelism between the ease of

17. Larson, E.: The Effect of Posterior Pituitary Preparations on the Large Intestine of the Unanesthetized Dog, J. Pharmacol. & Exper. Therap. **72**:363, 1941.

18. Ackerman, R. F.; Curl, H., and Crandall, L. A., Jr.: Gastrointestinal Tract Motility in the Absence of Bile, Am. J. Physiol. **134**:32, 1941.

19. Quigley, J. P., and Meschan, I.: Inhibition of the Pyloric Sphincter Region by the Digestion Products of Fat, Am. J. Physiol. **134**:803, 1941.

20. Tidwell, H. C., and Cameron, E. A.: The Relation Between the Chemical Structure of Fats and Their Ability to Produce Gastric Inhibition, Bull. Johns Hopkins Hosp. **70**:362, 1942.

absorption of a fat and its ability to produce gastric inhibition, which suggests that the absorption of fat from the duodenum is a prerequisite for the liberation of enterogastrone.

Tennent [21] concludes from animal experiments that alcohol delays gastric emptying and accordingly the absorption of dextrose. This delay in gastric emptying is attributed to the appearance of pylorospasm, which the author does not consider solely due to the irritating effect of alcohol on the gastric mucosa. When one considers that in these experiments the alcohol was administered by the intraperitoneal route, it seems pertinent to question whether the peritoneal irritation itself may not have contributed to alterations in motor activity. This may not have been the case, however, inasmuch as a certain length of time was allowed for the effects of alcohol to develop fully (intoxication) before dextrose was administered.

A comparison of the effect of liquid and of solid meals on intestinal activity has been made by Grindlay and Mann,[22] with observations on exteriorized loops of various portions of the small bowel. Sham feedings, the introduction of water and various liquid meals and the feeding of solid cooked meals all caused a typical sudden burst of motor activity, which was maintained, however, for more than a few minutes only in the case of a solid meal. Motor activity disappeared within a few minutes with a sham feeding and diminished rapidly after the administration of water or various liquids. The appearance of low grade, irregular segmentation waves and inconspicuous tonus changes was maintained for about half an hour in the case of water and slightly longer in the case of liquid meals. The motor response was sustained for hours after a solid meal, with resulting prominent irregular segmentation waves, tonus changes, tonus waves and occasional peristaltic waves, activity persisting in some instances for as long as twenty-four hours.

The effect of sodium amytal on gastric emptying was shown by Van Liere and Northup,[23] who noted an average decrease of almost 20 per cent when this drug was taken a short time before eating. An addition to studies on the effects of some spasmolytic substances on gastric function is to be found in the work of Lehmann and Knoefel.[24] A

21. Tennent, D. M.: The Influence of Alcohol on the Emptying Time of the Stomach and the Absorption of Glucose, Quart. J. Med. **2**:271, 1941.

22. Grindlay, J. H., and Mann, F. C.: Effect of Liquid and Solid Meals on Intestinal Activity, Am. J. Digest. Dis. **8**:324, 1941.

23. Van Liere, E. J., and Northup, D. W.: The Effect of Sodium Amytal on the Emptying Time of the Normal Human Stomach, J. Pharmacol. & Exper. Therap. **73**:142, 1941.

24. Lehmann, G., and Knoefel, P. K.: The Effects of Some Spasmolytic Substances on Gastric Function, J. Pharmacol. & Exper. Therap. **74**:217, 1942.

comparison of the effects of atropine and similar substances on experimental cardiospasm and on gastric hypermotility caused by insulin was made. The comparative potency of such compounds seemed to vary similarly with their potency in depressing motility of the small intestine and with their potency in antagonizing the spasmogenic effects of acetylcholine on isolated intestine. Particular attention was paid to one compound (diethylaminoethylfluorene-9-carboxylate hydrochloride) chosen from a series of forty-four related compounds as the most promising for clinical trial. It was found that in terms of atropine this compound was about one-twentieth as potent in reducing gastric hypermotility and had much less effect in delaying gastric emptying and in reducing gastric secretion when given in one hundred times the dose. Such studies are of extreme importance in view of the fact that a real shortage of atropine and atropine derivatives exists at present because of the war. It is obviously important to procure potent spasmolytic substances to replace atropine if possible. An additional result of the foregoing studies is of interest as confirmation of previous observations, namely, that atropine and similar substances have little or no relaxing action on experimental cardiospasm. Such a finding is entirely confirmatory of the failure of atropine to produce beneficial effects in "cardiospasm" in human beings.

The effects of senescence on gastric motility have been studied by Van Liere and Northup.[25] By comparison with standards previously obtained on a large group of vigorous young adults, it was possible to conclude that no alteration of gastric emptying time could be demonstrated in a group of old men. The average age of the subjects was 70 years. In view of increased interest in geriatrics, such a study is of fundamental importance.

A comparative study on the mechanism of the action of prostigmine on intestinal motility was made on human beings and on dogs by Schwartz, Reingold and Necheles.[26] Their observations were made by means of kymographic records obtained after the introduction of a balloon into an intestinal fistula in human beings and by a somewhat similar maneuver in animals. The increased motor activity, which lasted from thirty to sixty minutes, that was noted in the human subjects after the use of prostigmine was not altered by the addition of acetylcholine. There were no serious or disturbing by-effects from the prostigmine. In the animal experiments it appeared that the effects of prostigmine on the intestinal musculature were twofold, namely, through stimulation

25. Van Liere, E. J., and Northup, D. W.: The Emptying Time of the Stomach of Old People, Am. J. Physiol. **134**:719, 1941.

26. Schwartz, A. H.; Reingold, I., and Necheles, H.: A Study on the Mechanism of Action of Prostigmine on Intestinal Motility in the Human Being and in the Dog, Surgery **11**:746, 1942.

of the parasympathetic nerves and through direct stimulation of the intestinal musculature. It was impossible to abolish the action of prostigmine by the use of atropine, although the effect obtained by acetylcholine could be so abolished. The therapeutic use of prostigmine in paralytic ileus is thus justified by these investigators, who suggest a dose of prostigmine based on the weight of the individual patient. Patients weighing under 125 pounds (57 Kg.), they believe, should receive proportionately less than 1.0 mg. of prostigmine methylsulfate, a dose which seems to be adequate for persons at or above that weight.

Because of its application to optimum preparation of subjects for roentgen examination of the colon the study of Bruck and Fruchter[27] is of interest. Control observations were made on a group of 15 young adults after the ingestion of a barium sulfate meal, and subsequently repeated observations were made after the administration of a barium sulfate meal combined with one of several commonly used laxatives. The effects of fluidextract of cascara sagrada, compound licorice powder, magnesium citrate, magnesium sulfate and castor oil were thus studied. The last three laxatives produced some delay in gastric emptying time, and all of the laxatives studied produced an initial irritability of the proximal portion of the jejunum, lasting one to three hours. With magnesium sulfate there was a definite delay in the passage of the meal through the small intestine, but the other laxatives produced moderately increased motility of the small intestine. Of the preparations used, compound licorice powder and castor oil proved the most satisfactory in completely emptying the colon and are to be preferred for colonic cleansing in routine preparation for roentgen studies. In spite of the production of numerous bowel movements more barium sulfate was retained at the end of forty-eight hours after the administration of magnesium salts than during a control observation. These studies are supplementary to observations reported previously by Oppenheimer and Mann and reviewed a year ago.[28]

Necheles and Olson[29] report the effects of trauma and traumatic shock on gastrointestinal motility and secretions, and the results of this study are compared with those previously obtained on the effects of burns, after which there was an increase of gastric motility and in some animals a considerable increase in the volume and the acidity of the

27. Bruck, S., and Fruchter, J. M.: Influence of a Single Dose of Commonly Used Laxatives on Gastro-Intestinal Motility: A Comparative Study, Radiology **38**:145, 1942.

28. Jones, C. M.: Gastroenterology: A Review of Literature from July 1940 to July 1941, Arch. Int. Med. **68**:763 (Oct.) 1941.

29. Necheles, H., and Olson, W. H.: Experimental Investigation on the Effects of Trauma and Traumatic Shock on Gastrointestinal Motility and Secretions, Am. J. Physiol. **136**:32, 1942.

gastric secretions. In these experiments gastric motility was slightly increased for short periods when the blood pressure of traumatized animals was above 80 mm. and for somewhat longer periods and to a greater extent when the blood pressure declined further. This did not compare with the intensity of gastric activity that was noted after burns. In none of the burn experiments was there a depression of gastric motility, a phenomenon which was encountered in a number of the experiments with trauma. The authors believe that the moderate increase in gastric motility following traumatic shock may be related to anoxemia as both became more apparent with a lower blood pressure, but they point out that the anoxemia of the stomach may be more dependent on vasomotor regulation than on systemic blood pressure. Various degrees of traumatization had no significant effect on the gastric secretion, and the depressant effect of burns on salivary, pancreatic and biliary secretions was considerably greater than that associated with mechanical trauma. It would seem pertinent to point out that such animal experiments necessarily fail to take into account the factor of pain which is almost always associated with traumatic shock or severe burns in human beings. This cannot be entirely disregarded as a possible important factor in the production of various vasomotor disturbances, which might lead to motor or secretory changes in the stomach and thus have a bearing on the production of ulcer.

Studies by Wasteneys, Crocker and Hamilton[30] made use of an ingenious reentrant fistula in dogs, situated just below the junction of the duodenum and the jejunum, as a means of investigating the digestion of various food substances. Of the observations and suggestions reported, one is extremely pertinent; namely, it is not justifiable to interpret "emptying time" (as obtained from roentgen studies) in terms of relative digestibility of food stuffs. It is obvious from the numerous reports that have been made on gastric emptying time after roentgen studies and on the determination of "percentage of digestion," that conclusions based on what is largely a motor function are in no way adequate to cover entirely the question of digestion and digestibility.

Secretory.—A most competent discussion of the internal secretions of the gastrointestinal tract is to be found in an article by Ivy.[31] This article brings up to date the known facts in regard to this phase of the physiology of the digestive tract and outlines the implications, therapeutic and otherwise, in a satisfactory manner. The work is too detailed

30. Wasteneys, H.; Crocker, B. F., and Hamilton, P.: Studies of Digestion in the Dog, Am. J. Physiol. **135**:6, 1941.

31. Ivy, A. C.: Glandular Physiology and Therapy: Internal Secretions of the Gastrointestinal Tract, J. A. M. A. **117**:1013 (Sept. 20) 1941.

to warrant complete discussion in the present review but deserves a careful reading by those interested in the physiology of the gastrointestinal tract. The secretory response of the gastric glands to gastrin, the stimulation of pancreatic secretion by secretin, the evacuation of the gallbladder by cholecystokinin, the inhibition of gastric motility and secretion by enterogastrone, the stimulation of the secretion of succus entericus and the possible augmentation of the movements of the intestinal villi to promote intestinal absorption by villikinin are all discussed as proved or probable physiologic examples of the humoral control of the digestive processes. Mention is also made of the possibility that the gastrointestinal tract may harbor an "insulin synergist" affecting carbohydrate metabolism. This hypothetic substance, for which the name duodenin has been suggested, is supposed to have a stimulating effect on the islands of the pancreas. Ivy points out correctly that none of the internal secretions of the gastrointestinal tract has been demonstrated to have therapeutic value. Histamine, if it is gastrin, and secretin possess diagnostic value; cholecystokinin is of potential diagnostic value; enterogastrone and urogastrone (*vide infra*) possess therapeutic promise. In a discussion of the humoral stimulation of gastric secretion, Gregory and Ivy [32] present evidence that there are at least two components in the humoral stimulation of a transplant of the gastric fundus by a meal—one liberated from the gastric mucosa by the presence of secretagogues and the other from the mucosa of the small intestine by the presence of food or secretagogues. The results of experiments in which the mucosa of one or the other of the pouches of a two pouch preparation was anesthetized by procaine hydrochloride have provided evidence that the gastric component of humoral stimulation is hormonal in nature. No such experiments have been performed in connection with the intestinal phase. The result of one experiment, which is subject to confirmation, in which the pyloric region of the gastric mucosa was removed from the main gastric pouch of the two pouch preparation, leads to the conclusion that the presence of this region of the stomach in the main gastric pouch is not essential for the demonstration of the humoral response of the transplant to perfusion of the main gastric pouch with a solution of secretagogues. It would seem that confirmation of this particular phase of the experiment might have an important bearing on the question as to how much of the stomach is to be removed at subtotal resection in order to obtain the most favorable results from the point of view of acid secretion.

A further theoretic discussion on the role of enterogastrone, a substance obtained from the intestinal mucosa and one which inhibits gastro-

32. Gregory, R. A., and Ivy, A. C.: The Humoral Stimulation of Gastric Secretion, Quart. J. Exper. Physiol. **31**:111, 1941.

intestinal motility and secretion, is given by Quigley,[33] who emphasizes the necessity for further studies on the physiologic activity of this substance before attempting to assess any possible therapeutic value it may have in the therapy of ulcers. Further investigations on the gastric secretory depressant occurring in urine are presented by Friedman and Sandweiss.[34] These investigators observed the effect of this substance on gastric secretion in dogs with Heidenhain pouches and found that it inhibited the gastric secretion stimulated by insulin, histamine and food. They believe that the mechanism involved is not known but that the site of action is on the gastric secretory cells. The preliminary acute experiments showed the inhibitory effect to be absent in dogs which have had the whole of the small intestine removed, suggesting that such action on the gastric glands is indirect. The authors point out that a consideration of the available data published by themselves, by Ivy and his associates and by Necheles leads to the conclusion that a substance which inhibits gastric secretion when administered intravenously is excreted in the urine of normal men and women and in that of dogs. They believe that this inhibitory effect of urine extract is not due to pyrogenic substances. The nature of the gastric secretory depressant substance is unknown, but because it is relatively thermostable it does not appear to be an enzyme. It has not yet been proved that the integrity of the small intestine is essential for the inhibitory effect of enterogastrone, although it appears that the inhibitory effect of urogastrone is mediated by the small intestine. Gray and his collaborators[35] have been led to the conclusion that there is no support for the view that urogastrone and enterogastrone are identical. The evidence suggests the importance of the gastrointestinal tract for the regulation of urogastrone excretion. That the output of urogastrone is reduced below normal in patients with ulcer is apparently a proved fact. The action of urogastrone is apparently specific for the stomach, for it is without effect on salivary secretion and on urinary secretion. Both in animals and in man Gray and others have shown that this principle, when given parenterally, reduces the volume and the acidity of gastric secretion after the administration of histamine. Whether the same agent is responsible for mild motor inhibition as well has not been established.

33. Quigley, J. P.: Enterogastrone—Significant Steps in Development of the Present Conceptions, Am. J. Digest. Dis. **8**:363, 1941.

34. Friedman, M. H. F., and Sandweiss, D. J.: The Gastric Secretory Depressant in Urine, Am. J. Digest. Dis. **8**:366, 1941.

35. Gray, J. S.; Culmer, C. U.; Wells, J. A., and Wieczorowski, E.: Factors Influencing the Excretion of Urogastrone, Am. J. Physiol. **134**:623, 1941. Gray, J. S.: Present Status of Urogastrone, Am. J. Digest. Dis. **8**:365, 1941. Gray, J. S.; Wells, J. A., and Ivy, A. C.: Gastric Secretion in Enterectomized Dogs ibid. **8**:353, 1941.

The apparent excretion of urogastrone is decreased by removal of the small bowel, but there is no proof as yet that the inhibitory principle occurring in urine originates entirely in the small intestine, and it is quite possible that this is not the case. The obvious therapeutic implications inherent in this substance, which inhibits gastric secretory, and possibly motor, function, have yet to be explored from the point of view of prevention or cure of ulcer.

Sandweiss and Friedman [36] have studied the effect on histamine-stimulated gastric secretion in Mann-Williamson dogs of the gastric secretory depressant factor in extracts of urine of normal and of pregnant women. The range of gastric acidity was the same both in the treated and in the untreated animals, and it would appear that the prolongation of survival time in the treated animals was not due to the inhibition of gastric acid but to the administration of the urine extract. These authors suggest that the urine extracts exert beneficial effects through stimulation of active fibroblastic proliferation and epithelialization of the ulcer, a process which can occur in the presence of normal gastric acid juice. A good deal of careful and discriminating work must be done before the final status either of urogastrone or of enterogastrone can be determined, but it is obvious that this type of physiologic approach to the ulcer problem may well be of fundamental importance.

Further evidence of the influence of hormonal control of gastric secretion is to be found in experiments of Schiffrin,[37] who studied the relation between the parathyroid and the gastric glands in dogs. As has already been shown, the administration of parathyroid in amounts sufficient to increase calcium in the blood serum to any important degree produced a decrease in the volume and the acidity of the gastric contents after stimulation by histamine or by a test meal, and such an inhibition persisted after the serum calcium had returned to normal levels. Experiments were made on a Pavlov pouch dog and on a dog with an esophagotomy and a gastric fistula. The volume of the response to sham feeding and to administration of insulin and histamine was decreased, although there were no persistent after-effects, as in the previous experiment. In both instances, however, the concentration of pepsin in the gastric juice was definitely increased. In a Heidenhain pouch dog, such measures, on the other hand, increased the volume, the acidity and the chloride content of the gastric juice but had no effect on pepsin, and a similar effect was observed after the use of irradiated ergosterol. After thyroparathyroidectomy the volume of gastric secre-

36. Sandweiss, D. J., and Friedman, M. H. F.: Is the Beneficial Effect of Urine Extracts on Mann-Williamson Ulcers Due to the Gastric Secretory Depressant in Urine? Am. J. Digest. Dis. **9**:166, 1942.

37. Schiffrin, M. J.: Relationship Between the Parathyroid and the Gastric Glands in the Dog, Am. J. Physiol. **135**:660, 1942.

tion was increased and the concentration of pepsin was decreased in all of the different preparations, but this result could be reversed by the intravenous injection of calcium lactate or the subcutaneous administration of solution of parathyroid. Thyroxin had no effect on the gastric secretory response.

A rather interesting gastroscopic observation on gastric secretory activity was made by Lerner, Asher and Andrews.[38] They watched the appearance of neutral red in the gastric mucosa after parenteral injection of the substance. In fasting animals only scattered pinpoint areas could be seen, and they were limited almost entirely to the fundus and the upper portion of the body. No dye was seen at the cardia, antrum or pylorus. It would seem from this observation that in the fasting state few of the pepsin-secreting and hydrochloric acid–secreting cells were functioning, a not illogical but nevertheless interesting finding.

By means of careful experiments on dogs with vagotomized gastric pouches, Gray and Bucher[39] made a detailed study of the composition of the gastric juice as a function of the rate of secretion. Repeated injections of histamine provided the stimulus for secretory activity, and accurate determinations of basic and of acid ions were obtained. By a detailed analysis of these various components, it was shown that the composition of gastric juice can vary only between the limits set by its two main sources—the parietal and the nonparietal cells. Since the nonparietal component is secreted at a slow and practically constant rate, whereas the parietal component is secreted at rates which vary widely with the dose of histamine, the authors conclude that the composition of the gastric juice is a function of its rate of secretion. The only constant element was that of potassium, the concentration of which remained practically the same throughout the observations.

In experiments on animals with cannulated gastric and duodenal fistulas, Berk, Thomas and Rehfuss,[40] studied the reaction and neutralizing ability of the pyloric antrum and the first portion of the duodenum after high carbohydrate and high fat meals. With an Ewald meal the contents of the first portion of the duodenum displayed a neutral-

38. Lerner, H. H.; Asher, L., and Andrews, K.: The Excretion of Neutral Red by the Gastric Mucosa as Visualized Gastroscopically, Am. J. Digest. Dis. **9**:109, 1942.

39. Gray, J. S., and Bucher, G. R.: The Composition of Gastric Juice as a Function of the Rate of Secretion, Am. J. Physiol. **133**:542, 1941.

40. Berk, J. E.; Thomas, J. E., and Rehfuss, M. E.: The Reaction and Neutralizing Ability of the Contents of the Pyloric Antrum and First Part of the Duodenum in Normal Dogs Following an Ewald Meal, Am. J. Physiol. **136**:157, 1942; The Effect of a Cream Meal on the Acidity and Neutralizing Ability of the Contents of the Duodenal Bulb in Normal Dogs, ibid. **136**:285, 1942.

izing, buffering and diluting capacity apparently in excess of physiologic needs, p_H values in both the pyloric antrum and the duodenal bulb varying independent of titratable total acidity. A high fat feeding, as is known, diminished gastric acidity and enhanced the excess neutralizing ability of the contents of the first portion of the duodenum over fairly prolonged periods. The authors feel that this decrease in duodenal acidity following the administration of cream was only partly due to the inhibitory effect of fat on gastric secretion. They believe that the acidity of the contents of the duodenal bulb in a normal dog is largely determined by the type of food undergoing digestion and is related only in part to the acidity of the gastric contents. In a normal dog cream appears to be a much more effective duodenal antacid than some of the commonly employed antacid medications. Such results, however, await the further elucidation that may possibly be obtained from a more accurate knowledge of the inhibitory effects of such substances as enterogastrone. Another method of approaching the subject of gastric secretory activity is described by Mann, Grindlay and Mann.[41] By an ingenious operative procedure on dogs it was possible to make chloride determinations on arterial and on gastric venous blood during the process of digestion. During the rapid secretion of hydrochloric acid by the gastric mucosa appreciable differences in the chloride concentration in the systemic and the gastric venous blood were observed only occasionally. These differences appeared to depend mainly on variations in the cell chlorides.

Grant [42] has contributed further information on the buffering substances in gastric secretion by studies on gastric mucus. In cats she found that mucus from surface epithelial cells and from the cells producing it in the vagal type of secretion is an immediate source of calcium in gastric secretions. Actively functioning peptic or parietal cells do not appear to be necessary for its production. The theory that mucus is an important factor for the reduction of gastric acidity is supported by direct evidence. She has been led to believe that an important factor responsible for variations in calcium content and acidity of gastric secretions in the presence of varying amounts of mucus in secretions of different types. Calcium is liberated from the mucus in a reaction associated with the reduction of acidity and is an index of this reaction. Further evidence that the mucoid secretion of the stomach is of importance in lowering the acidity and the total chloride concen-

41. Mann, F. D.; Grindlay, J. H., and Mann, F. C.: The Withdrawal of Chloride from the Blood by the Gastric Glands, Am. J. Digest. Dis. **8**:451, 1941.

42. Grant, R.: Calcium in Gastric Mucus and Regulation of Gastric Acidity, Am. J. Physiol. **135**:496, 1942.

tration of the gastric juice was obtained by Babkin and his associates [43] as a result of the application of acetic acid solutions to the gastric mucosa. When this procedure was followed by the injection of histamine, a diminished volume of gastric secretion, with a lowering of the total chloride concentration and the free and the total acidity, was constantly noted, and this was associated with a striking increase in mucus secretion, which the authors believe was responsible for the alterations obtained. Certainly such findings would seem to indicate clearly one of the protective mechanisms inherent in the stomach that is more or less effective in the presence of mucosal irritation or inflammation, as previously pointed out by Fogelson and others.

Sixteen amino acids were studied by Thomas [44] to determine whether they caused gastric inhibition when placed in the small intestine. Only the monoamino-monocarboxy acids caused gastric inhibition regularly when administered in neutral salts, and the inhibitory effect was roughly proportional to their molecular weights. The dicarboxy acids and the diamino acids inhibited secretion only when administered as free acids without neutralization.

The effect of heavy irradiation of the stomach is well known to decrease its secretory activity, and observations made by Streicher [45] showed that pathologic changes following such a procedure involved chiefly the secretory epithelium of this organ. He also produced evidence that hepatic damage secondary to direct high voltage irradiation or caused by the use of carbon tetrachloride not only produced intrahepatic changes but, at the same time, depressed the acidity of the gastric juice. In these experiments the gastric juice obtained from a Pavlov pouch was apparently highly buffered, and it appeared that this buffering again was due to chemical constituents (perhaps protein) which were recognizable at hydrogen ion concentrations between 3 and 5 and between 6 and 7.

A study of the functions of the stomach following partial pyloric obstruction with and without gastroenterostomy was made by Neuwelt and associates [46] after an operative procedure on dogs. After a prolonged control period of observation following the production of pyloric stenosis, gastroenterostomies were performed and gastric secretory activity was

43. Babkin, B. P.; Hebb, C. O., and Krueger, L.: Changes in the Secretory Activity of the Gastric Glands Resulting from the Application of Acetic Acid Solutions to the Gastric Mucosa, Quart. J. Exper. Physiol. **31**:63, 1941.

44. Thomas, J. E.: Gastric Inhibition Caused by Amino Acids in the Small Intestine, Am. J. Physiol. **135**:609, 1942.

45. Streicher, M. H.: Effect of Hepatic Damage on Gastric Acidity, Arch. Surg. **43**:74 (July) 1941.

46. Neuwelt, F.; Medoff, J.; Patredjl, J., and Necheles, H.: A Study of the Functions of the Stomach Following Pyloric Obstruction and Gastro-Enterostomy, Am. J. Digest. Dis. **8**:310, 1941.

compared with that during the control period. The results were variable. There was no change in the volume or the acidity in some animals after enterostomy; in others there was an increase, and in a third group, a decrease. Neither peptic nor anastomotic ulcers were observed in any of the animals. The conclusion was reached that gastroenterostomy in dogs combined with partial pyloric stenosis cannot be relied on to produce rapid emptying of the stomach or reduced gastric acidity. Such a finding may help to explain many of the failures attributed to a gastroenterostomy in the presence of ulcer, but a complete comparison is not entirely permissible, inasmuch as none of these dogs had an ulcer at any time.

A rather complete review of the various experimental procedures that have been carried out on the stomach in an attempt to produce pernicious anemia has been made by Petri and Jensenius.[47] As these authors point out, no operative procedures on animals have been developed which will result in the production of a pernicious anemia state, although various types of anemia, depending on the species of animal and kind of operation, have resulted from various maneuvers. Because of the discrepancy existing between results obtained by various investigators, the writers urge a still further study of the biologic foundation underlying such a condition as addisonian anemia. They consider that failure to reproduce such a condition in animals is due to the fact that either the site of formation of the intrinsic factor has not been adequately controlled by operative procedures or the correctness of Castle's theory has to be questioned. Fox and Castle,[48] using various preparations of hog and of human stomach, have attempted to determine whether the material present in the preparations and possessing a blood-forming activity in addisonian pernicious anemia could be used to define the site at which the intrinsic factor was secreted and whether observations based on the hog stomach were applicable to the human stomach. From their observations and those of Meulengracht it appears that the antianemic potency of the pyloric portion of the hog stomach indicates the main site at which the intrinsic factor is secreted in that animal but that in man areas containing the fundus type of gland and not the "pyloric gland organ" are the important sites at which the intrinsic factor is secreted. This site coincides with the site of the degenerative process seen in microscopic preparations of the stomach in pernicious anemia in human beings. It is important to stress such

47. Petri, S., and Jensenius, H.: Experimental Studies on Production of Pernicious Anemia by Operation on Digestive Tract: Survey of Results of Total Gastrectomy and Resections of Stomach, Acta med. Scandinav. **106**:274, 1941.

48. Fox, H. J., and Castle, W. B.: Observations on Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: IX. Difference in Site of Secretion of Intrinsic Factor in Hog and in Human Stomach, Am. J. M. Sc. **203**:18, 1942.

species differences in relation to animal experimentation, and such a finding, of course, would seem to explain the infrequency with which macrocytic anemia occurs in gastric resections in man, inasmuch as under such circumstances the cardiac portion of the human stomach is saved and may provide an adequate source of the intrinsic factor. In spite of the known secretory deficiencies existing in patients with addisonian pernicious anemia, it is of some interest that Witebsky and associates [49] were able to demonstrate that the gastric juice of patients with pernicious anemia contains blood group–specific substances in the same large amounts as normal gastric juice.

Absorptive.—The complicated process of phosphorylation in relation to intestinal absorption still requires much study before it can be finally elucidated. To those interested in this complex and still hypothetic phenomenon the study of Beck [50] on some of the details of the phosphorylation hypothesis of dextrose absorption by intestinal mucosa warrants examination. In this work an analysis was made of various phosphate fractions in intestinal mucosa after absorption in order to determine the relative importance of various phosphorus compounds in dextrose absorption. On the basis of barium separation procedures and "fructose" determinations it seemed that most of the absorptive increase in the intestinal mucosa was due to an accumulation of a hexose monophosphate ester.

Barnes, Miller and Burr,[51] using spectroscopically distinguishable conjugated fatty acids of corn oils, made a study of the absorption and transport of the methyl esters of fatty acids across the intestinal mucosa of rats. The results showed no apparent parallelism between the rate of fatty acid incorporation into mucosa phospholipids and transport. Winter and Crandall,[52] by using the angiostomy technic in dogs, have thrown some new light on the question of the portal absorption of fatty acids, samples of blood being drawn simultaneously from the portal and the hepatic vein and from the femoral artery before and during fat absorption. No significant arterioportal or hepatic inflow-outflow differences in fatty acid content could be demonstrated during fat absorption. It would seem from such results that fat absorption from the intestine by way of the portal vein is negligible.

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49. Witebsky, E.; Klendshoj, N. C., and Vaughan, S. L.: Occurrence of Blood Group Specific Substances in Gastric Juice of Patients with Pernicious Anemia, Proc. Soc. Exper. Biol. & Med. **49**:633, 1942.

50. Beck, L. V.: Organic Phosphate and "Fructose" in Rat Intestinal Mucosa, as Affected by Glucose and Phlorhizin, J. Biol. Chem. **143**:403, 1942.

51. Barnes, R. H.; Miller, E. S., and Burr, G. O.: The Absorption and Transport of Fatty Acids Across the Intestinal Mucosa, J. Biol. Chem. **140**:233, 1941.

52. Winter, I. C., and Crandall, L. A., Jr.: The Question of the Portal Absorption of Fatty Acids, J. Biol. Chem. **140**:97, 1941.

Alterations in the absorptive capacity of the small intestine in the presence of deficiency disease are known to occur and undoubtedly form the basis of some of the nutritional disturbances seen in such conditions. The study of Beams, Free and Glenn [53] on the absorption of galactose from the gastrointestinal tract in deficiency diseases adds further confirmation of these known facts. In patients with active pellagra and nontropical sprue there was marked impairment of galactose absorption. Curiously enough, a distinct improvement in the absorption of galactose accompanied clinical improvement in patients with pellagra but not in those with sprue. Two of 4 patients with rosacea keratitis showed decreased galactose absorption, which improved under riboflavin therapy. Any study of deficiency conditions should include a consideration of celiac disease. For this reason the work of May and McCreary [54] deserves mention. A deficient absorption of vitamin A is a constant feature of celiac disease, but this fact is of limited value in differentiating it from other conditions producing the celiac syndrome. The level of carotenoids in the blood of patients with celiac disease seems to follow the clinical course of the disease, being low throughout the active stage and rising with clinical improvement. The absorption of vitamin A appears to return to an entirely normal level when recovery is complete.

MacKay and Clark [55] showed that the rate of absorption of dextrose from the rat intestine under conditions of forced feeding depended on the amount and concentration of sugar. Variable doses administered in a fixed volume gave a relatively constant absorption coefficient, but when variable doses of dextrose were administered at the same concentration but in variable volumes, the absorption coefficient was related to the dose of dextrose. By concentrating the period of eating through a prior period of fasting or by giving dextrose alone and increasing the appetite with injections of protamine zinc insulin or by the use of a cold environment, a great increase in the absorption coefficient was obtained. Anoxia up to and including a partial pressure of oxygen equivalent to an altitude of 28,000 feet (8,400 meters), according to Northup and Van Liere,[56] did not significantly alter the absorption of dextrose from the small intestine of the dog, although it did exert a significant

53. Beams, A. J.; Free, A. H., and Glenn, P. M.: The Absorption of Galactose from the Gastro-Intestinal Tract in Deficiency Diseases, Am. J. Digest. Dis. **8**:415, 1941.

54. May, C. D., and McCreary, J. F.: The Absorption of Vitamin A in Celiac Disease: Interpretation of the Vitamin A Absorption Test, J. Pediat. **18**: 200, 1941.

55. MacKay, E. M., and Clark, W. G.: The Rate of Glucose Absorption from the Intestine of the Rat, Am. J. Physiol. **135**:187, 1941.

56. Northup, D. W., and Van Liere, E. J.: The Effect of Anoxia on the Absorption of Glucose and of Glycine from the Small Intestine, Am. J. Physiol. **134**:288, 1941.

depressing action on the absorption of aminoacetic acid. This experiment suggests that possibly an oxidative process is directly involved in the absorption of aminoacetic acid. Driver [57] studied the effect of hexylresorcinol and other agents on the absorption of sugars, chloride and sulfate from the alimentary tract. His results indicate that hexylresorcinol and ammonium thiocyanate inhibit the activity of carbonic anhydrase in vitro and that both lower the absorption of chloride from the alimentary tract. He believes that there is a special mechanism for at least a part of chloride absorption and that carbonic anhydrase may be involved, along with a structural arrangement favorable for the absorption of the ion. The absorption of sulfate likewise is probably partly dependent on some biologic agent. Peters [58] observed that the intestinal absorption of chloride, water and sulfate was appreciably diminished by the administration of bile salts, which in some instances actually produced a transfer of chloride and water toward the intestinal lumen. Werch and Ivy [59] concluded that a negligible amount, if any, of galacturonic acid is absorbed from either the small or the large intestine of dogs or from that of human beings.

One aspect of the absorption of undigested protein from the intestinal tract is presented by Harten, Livingston and Walzer.[60] Their studies have a particular bearing on the question of food allergy. A cutaneous site on a rhesus monkey was sensitized by the intracutaneous injection of human serum containing skin-sensitizing antibodies. After an interval of twenty-four to forty-eight hours to permit fixation of the antibodies at the cutaneous site, the specifically related antigen was administered orally. The lighting up of the sensitized cutaneous site with an urticarial reaction within a few minutes marked the entrance of unaltered protein into the circulation. The authors believe that experimental evidence now exists which indicates that antigens may be absorbed from any part of the intestinal tract, though the rate of absorption may vary somewhat in different organs. The amount of antigen necessary to produce the allergic reaction has been shown to be infinitesimally small. The "absorption time" of the cottonseed protein utilized in these experiments was only two minutes from the stomach,

57. Driver, R. L.: Effects of Hexylresorcinol and Other Agents on the Absorption of Sugars, Chloride and Sulfate from the Alimentary Tract, Am. J. Physiol. **135**:330, 1942.

58. Peters, H. C.: The Influence of Bile Salts on Active Intestinal Absorption of Chloride, Am. J. Physiol. **136**:340, 1942.

59. Werch, S. C., and Ivy, A. C.: Is Galacturonic Acid Absorbed by the Small and Large Intestine? Proc. Soc. Exper. Biol. & Med. **48**:9, 1941.

60. Harten, M.; Livingston, S., and Walzer, M.: Studies in Absorption of Undigested Protein: IX. Absorption from the Stomach and Esophagus, J. Lab. & Clin. Med. **27**:56, 1941.

whereas the "absorption time" of the same protein from the esophagus was apparently ten minutes.

The relation of the p_H of intestinal contents to calcium and phosphorus utilization was studied by Jones [61] in rats. The data obtained tend to throw considerable doubt on the theory that an increase in intestinal acidity provides the basis by which fats beneficially influence calcification. Lard, oleic acid, and vitamin D all increased the acidity of the lower portion of the ileum and less consistently that of the cecum and the colon. All of these substances showed definite antirachitic activity. The administration of vitamin D produced the slightest lowering of p_H but at the same time was associated with the greatest antirachitic action. Intestinal p_H was increased by the addition of aluminum sulfate to a stock diet but resulted in severe rickets. The addition of dibasic sulfate to a low phosphorus rachitogenic diet protected the animals against rickets without changing the p_H of the intestinal contents, whereas lactose produced as much acidity in the intestine as did lard but did not show any antirachitic action.

Studies on the absorption of propylene glycol were made by Van Winkle.[62] He felt that the quantitative absorption of this substance by the digestive tract agreed in several respects with that demonstrated by other investigators previously for alcohol, phenol and iodide, except that the absorption of propylene glycol was more rapid and more complete.

An inconclusive study by Webster [63] on lead and arsenic absorption and excretion in man is of interest because it demonstrates the potential dangers incident to the use of lead arsenate in sprays. The observations were made on orchardists who ate varying numbers of sprayed apples daily. Analyses of samples of the fruit eaten showed a potential intake of 1 to 26 mg. of lead and 0.34 to 6.8 mg. of arsenic per person per day. Analyses of urine and stools showed that the largest part of the lead was eliminated in the feces, a finding in agreement with earlier experiments by Fairhall and Neal. In the present study the fecal output of arsenic equaled or exceeded the urinary output of arsenic in the majority of instances, although in the earlier experiments only traces of arsenic were regularly found in the feces. Two explanations were offered for this difference: (1) that the weathered spray residue may differ from pure lead arsenate in physical and chemical properties, and (2) that per-

61. Jones, J. H.: The Relation of the p_H of Intestinal Contents to Calcium and Phosphorous Utilization, J. Biol. Chem. **142**:557, 1942.

62. Van Winkle, W., Jr.: Quantitative Gastro-Intestinal Absorption and Renal Excretion of Propylene Glycol, J. Pharmacol. & Exper. Therap. **72**:344, 1941.

63. Webster, S. H.: Lead and Arsenic Ingestion and Excretion in Man, Pub. Health Rep. **56**:1359, 1941.

sons having chronic exposure to compounds containing lead and arsenic may differ from persons with only acute exposure in their utilization and excretion of arsenic. Because of the frequent occurrence of such an exposure to toxic materials throughout the country, it is to be hoped that further studies will be carried out.

Absorptive experiments by Melnick, Robinson and Field[64] on the fate of thiamine in the digestive secretions are of interest. Optimum absorption of thiamine in part is related to the presence of food in the stomach, which permits the vitamin to be retained for a longer period in that organ, thus enabling direct absorption and avoiding subsequent destruction in the more alkaline medium occurring in the small intestine. Normal acidity of the gastric chyme reduces the p_H of secretions in the duodenum, and this in turn again decreases the possibility of the destruction of the vitamin B_1 by the alkaline bile and pancreatic juice. An important corollary of the fact that thiamine is stable in normal gastric juice is that the oral administration of thiamine in conjunction with antacids is contraindicated if optimum utilization of the vitamin is desired. Studies on the absorption of thiamine from the intestine of rats have been carried out by Stockholm, Althausen and Borson.[65] Their observations seemed to indicate that phosphorylation does not play a dominant part in determining the rate of intestinal absorption of thiamine and that thyroxin does not have a stimulating effect on the rate of enzyme formation of the pyrophosphate ester. It would seem that the absorption of thiamine in the intestine probably takes place by means of simple diffusion and is roughly proportional to its concentration in the intestine.

CLINICAL ASPECTS

Mouth.—The incidence of chronic ulcerative lesions of the mouth has been carefully investigated in a large American clinic by Keyes,[66] who reports a study of 2,077 oral lesions. Of these, only 1 in 4 was benign. Of the 1,561 malignant lesions, all but 38 were squamous cell carcinomas, 1 instance of which was encountered in a boy aged 19. As a rule, the malignant lesions occurred in patients over 60 years of age in association with bad dental conditions or gingivitis or in edentulous old men who chewed tobacco or smoked a great deal. Leukoplakia commonly accompanied cancer of the buccal mucosa and was prone to occur within the cheek on the side in which the chewing tobacco was held.

64. Melnick, D.; Robinson, W. D., and Field, H., Jr.: Fate of Thiamine in the Digestive Secretions, J. Biol. Chem. **138**:49, 1941.

65. Stockholm, M.; Althausen, T. L., and Borson, H. J.: Mechanism of Intestinal Absorption of Thiamin, Proc. Soc. Exper. Biol. & Med. **46**:387, 1941.

66. Keyes, E. L.: Chronic Ulcerative Lesions of the Mouth: Incidence of Cancer in 2077 Cases at Barnard Hospital, Am. J. Surg. **56**:70, 1942.

Of the benign lesions, nearly one-third consisted in degenerative or inflammatory lesions. Little attention is paid, however, in this report to the occurrence of oral lesions secondary to vitamin deficiencies. The frequency with which the last-named type of lesion may be observed is of real clinical importance, not only because adequate therapy, as a rule, is entirely successful in relieving associated symptoms, but because it commonly suggests the presence of an underlying deficiency condition which might otherwise be missed. Rosenblum and Jolliffe [67] present an excellent summary of the oral manifestations of vitamin deficiencies, pointing out the various primary and contributory causes of such lesions. This paper constitutes an excellent résumé of present knowledge of buccal deficiency disease and is further enhanced by illuminating comments by Mackie. Further attention to oral lesions associated with dietary deficiencies appears in an article by Chapman and Harris,[68] who point out the importance of such deficiencies in conditioning inflammatory processes in the mouth. In monkeys maintained on certain vitamin-deficient diets there was noted a consistent tendency to oral lesions accompanied by an increase in the fusospirochetal flora. Furthermore, such animals maintained on an adequate stock diet tended to resist artificial implants of fusospirochetal flora under the severest of test conditions.

Damianovich and Ravizzoli [69] add further information in an article on stomatitis aphthosa. Nicotinic acid therapy proved highly successful in the treatment of a group of children presenting this condition. Beneficial results were obtained after the first few doses of nicotinic acid, and a cure was usually accomplished in three days, with rapid epithelization of the lesions. Gingivitis proved more refractory. The suggestion that infection of the mouth with organisms other than Vincent's may be associated with nicotinic acid deficency is also postulated by Walton and his associates.[70] Although such observations are by no means new, it is still not too generally recognized that avitaminosis frequently underlies the occurrence of annoying and at times serious buccal lesions.

Esophagus.—Passing comment is warranted on several articles on esophageal diseases, although nothing new has appeared in the literature of the past year. Clinical observations on the symptoms and signs asso-

67. Rosenblum, L. A., and Jolliffe, N.: The Oral Manifestations of Vitamin Deficiencies, J. A. M. A. **117**:2245 (Dec. 27) 1941.

68. Chapman, O. D., and Harris, A. E.: Oral Lesions Associated with Dietary Deficiencies in Monkeys, J. Infect. Dis. **69**:7, 1941.

69. Damianovich, J., and Ravizzoli, R.: Nicotinic Acid and Stomatitis Aphthosa, Arch. argent. de pediat. **16**:21, 1941.

70. Walton, C. H. A.; Graham, H. M., and Lansdown, L. P.: Acute Ulcerative Stomatitis: Three Unusual Cases, Lancet **2**:214, 1941.

ciated with stenosis of the upper portion of the esophagus are presented in a rather interesting fashion by Camiel and Loewe.[71] On physical examination more than one third of a small group of patients showed definitely clubbed fingers, probably secondary to aspiration of ingesta into the trachea or the bronchial tree. The authors suggest that the appearance of pulmonary lesions, paralysis of the vocal cords or clubbed fingers in the absence of a known primary source should point strongly to the possibility of disease of the upper portion of the esophagus.

Adverse comment is warranted on a report by Mitchell [72] of a case of achalasia of the esophagus. In this instance the condition was satisfactorily relieved by esophagogastrostomy. No mention is made of careful bouginage, however, and it would seem reasonable to suggest that in such cases this measure should always be attempted before resorting to such a serious surgical procedure as that reported by the author. That such conservatism in therapeusis is entirely warranted is indicated by a careful record of Hara and Rosenvold.[73] In this instance complete cicatricial atresia of the esophagus of six years' duration was successfully treated, after a temporary gastrostomy, by peroral esophagoscopy with dilatation. Such procedure is well established and whenever possible should be the therapy of choice.

Fibrosis of the esophagus with subsequent narrowing is thoroughly discussed by Mosher [74] in a paper based on an examination of 100 autopsy specimens. The article is of particular interest because of the percentage of carefully examined material. The role of infection due to local or distant sources is discussed, and certain points of interest are brought out. Thrombosed veins, periesophageal abscesses and similar conditions are considered, and an explanation is offered for the so-called "spasm" of the pylorus that is noted at birth. The author cites 3 cases in which at birth both the pyloric and the cardiac end of the stomach was narrowed. Although one cannot easily accept the author's ideas of prenatal infection, the pathologic material presented is of real clinical interest. An experimental study by Strong and Smith [75] is of importance in this connection. Experiments were carried out on a strain of mice in which there was practically no evidence of an inflammatory, parasitic

71. Camiel, M. R., and Loewe, L.: Syndrome of Upper Esophageal Stenosis, Ann. Int. Med. **15**:63, 1941.

72. Mitchell, H. E.: Achalasia of the Esophagus, with Report of a Case Relieved by Esophagogastrostomy, Ann. Otol., Rhin. & Laryng. **50**:662, 1941.

73. Hara, H. J., and Rosenvold, L. K.: Cicatricial Atresia of the Esophagus, Arch. Otolaryng. **34**:574 (Sept.) 1941.

74. Mosher, H. P.: Infection as a Cause of Fibrosis of the Esophagus, Ann. Otol., Rhin. & Laryng. **50**:633, 1941.

75. Strong, L. C., and Smith, G. M.: Stenosis of the Esophagus in Four Generations of Mice of the N. H. Strain, Yale J. Biol. & Med. **13**:489, 1941.

or neoblastic condition. Esophageal stenosis with proximal dilatation appeared several times in closely related individuals of this strain, and there seemed little doubt that a certain localized hyperplasia of the esophageal epithelium with active keratosis was probably the cause of the narrowing. These lesions were not observed at birth.

Cancer of the esophagus still presents a diagnostic and therapeutic challenge. The wisdom of more frequent and earlier esophagoscopic examination is properly stressed by Lindsay [76] as an early diagnostic procedure. To this suggestion should be added the fact that more than one esophagoscopic examination may be needed in some cases before biopsy material has been obtained that is adequate for diagnosis. This is due to the fact that the inflammatory involvement of the esophagus above the carcinomatous area frequently prevents adequate examination until skilful bouginage and dilatation have been performed, with resulting better exposure of the lesion. The results of surgical procedures are still unsatisfactory. An adequate summary of the present status of surgical treatment of esophageal cancer is presented by Sweet [77] and is of particular interest because of its complete discussion of the various methods that are at present available, including various types of gastrostomy and reconstruction operations. He states that the Beck-Jianu operation in the reconstruction of an external esophagus after resection in certain favorable cases of cancer of the esophagus has been tried in several instances, with satisfaction.

An unusual cause of esophageal obstruction is that reported by Gross and Freedman,[78] who record an instance of an occluding secondary carcinomatous tumor of the esophagus metastatic from clinically silent prostatic carcinoma.

Diaphragmatic Hernia.—Unusual manifestations of diaphragmatic hernias are recorded by Harrington [79] and Colmers.[80] In the 4 cases reported by Harrington, a complete hernial sac projected into the right thoracic cavity and, unlike most herniations on the right side, there was no history of previous trauma. In one of the 4 cases, in addition to a subcostosternal hernia, a second esophageal hiatus hernia was present. In 2 instances the hernial contents included omentum and bowel, and the

76. Lindsay, J. R.: The Early Diagnosis of Carcinoma of the Esophagus, Ann. Otol., Rhin. & Laryng. **50**:675, 1941.

77. Sweet, R. H.: Gastrostomy in Cases of Carcinoma of the Esophagus, Surg., Gynec. & Obst. **73**:55, 1941.

78. Gross, P., and Freedman, L. J.: Obstructing Secondary Carcinoma of the Esophagus, Am. J. Path. **18**:361, 1942.

79. Harrington, S. W.: Subcostosternal Diaphragmatic Hernias, Surg., Gynec. & Obst. **73**:601, 1941.

80. Colmers, R. A.: Parasternal Diaphragmatic Hernia with Report of a Case on the Right Side, Radiology **37**:733, 1941.

patients presented the usual symptoms of intermittent digestive disturbances and partial intestinal obstruction. In the other 2 cases, however, only omentum was contained in the hernial sac, and in the absence of typical symptoms a preoperative diagnosis of a malignant lesion was made. Operative procedures were successful in all 4 cases. The discussion in Colmers' report is of interest particularly in relation to the time of development of a parasternal diaphragmatic hernia on the right side. Because of the late development of symptoms and histologic changes in the adjacent pulmonary tissue, the author believes that the hernia was acquired in later life.

A study of the symptoms associated with small hiatus hernias is presented by Jones,[81] with special reference to the clinical differences between these small lesions, frequently recognized with difficulty by the roentgenologist, and the much larger herniations recorded in the earlier literature. Unlike many writers, the author believes that extremely small hernias may in certain instances form the basis of acute symptoms, which not infrequently are almost indistinguishable from those associated with coronary heart disease. A careful statistical analysis of symptoms observed in a group of private patients with relatively small hernias forms the basis of this report. That large hernias may at times cause symptoms simulating cardiac disease has long been recognized, but as a rule the symptoms are not those of angina pectoris. The source of such symptoms in larger hernias is almost certainly associated with mediastinal displacement with cardiac embarrassment. An excellent report is that of McGinn and Spear.[82] These authors record a case of diaphragmatic hernia in an 81 year old woman with postmortem observations. The clinical symptoms were those of acute cor pulmonale with marked cyanosis, dyspnea and electrocardiographic abnormalities. Compression of the lungs by an increase in the amount of stomach herniating through the diaphragm caused an acute strain on the right side of the heart. The exact mechanism involved in the production of anginal symptoms by lesions of the esophagus, stomach or gallbladder is still not thoroughly understood. Numerous attempts to elucidate the problem have been recorded in the literature since von Bergman's studies in 1932. Consideration of the various possibilities are to be found in the article by Jones (*vide supra*) and in one by Andrews [83] on cardiovascular disturbances in gastrointestinal diseases.

81. Jones, C. M.: Hiatus Esophageal Hernia, with Special Reference to Comparison of Its Symptoms with Those of Angina Pectoris, New England J. Med. **225**:963, 1941.

82. McGinn, S., and Spear, L. M.: Diaphragmatic Hernia Presenting the Clinical Picture of Acute Cor Pulmonale, New England J. Med. **224**:1014, 1941.

83. Andrews, C. L.: Cardiovascular Disturbances in Gastrointestinal Diseases, J. M. Soc. New Jersey **38**:305, 1941.

Gastritis and Gastroscopy.—As was to be expected since the introduction of the flexible gastroscope, the number of articles devoted to a consideration of gastritis and allied conditions has steadily increased. Much of the literature is still inconclusive or contradictory, but there is evidence of a widespread and earnest attempt completely to reevaluate the clinical and the experimental use of gastroscopy and the true clinical significance of gastritis.

Pathologic changes occurring in nutritional gastritis in rats are recorded by Berg.[84] The observations were carefully controlled, and it was found that in those animals placed on inadequate diets, gastritis could be produced in a relatively short time, with involvement of the antrum and the rumen separately or together. The pathologic changes in the mucosa of the antrum and those in the mucosa of the rumen were essentially similar and consisted in ulcerations in areas of epithelial hyperplasia that tended to undergo spontaneous healing. Recurrent necrosis and hemorrhage appeared to develop in healing defects and to lead to chronic changes. The fundus was relatively free of lesions, but those noted were essentially hemorrhagic erosions. Although such changes cannot be compared with certainty to those observed in deficiency disease in human beings, they should cause serious consideration as regards some of the potential factors in the causation of gastritis.

One of the obvious needs in a study of clinical gastritis as observed gastroscopically at the present time is a correlation between the gastroscopic findings and the results of histologic examination of biopsy specimens of the stomach obtained either at operation or at gastroscopy. Such studies are beginning to appear. Swalm and Morrison [85] compared gastroscopic and histologic observations of the stomach in patients with gastric and with extragastric disease during life and at autopsy and found that there was agreement between the two in about half of a small series of cases. In one fourth of the cases there was complete disagreement, and in a similar number there was only questionable conformity. These authors conclude that the gastroscopic appearance of severe gastritis is usually verified by histologic examination, but they point out the important fact that the gastroscopic appearance of a mild or moderate degree of gastritis or of a normal stomach may be contradicted by the histologic examination of a biopsy specimen. A somewhat similar study on a slightly larger group has recently been carried out by

84. Berg, B. N.: Pathological Changes in Nutritional Gastritis in Rats, Am. J. Path. **18**:49, 1942.

85. Swalm, W. A., and Morrison, L. M.: Gastroscopic and Histologic Studies of the Stomach with Gastric and Extra-Gastric Disease During Life and at Autopsy, Am. J. Digest. Dis. **8**:391, 1941.

Benedict and Mallory,[86] in which specimens of stomach obtained at the time of gastric resection were subjected to careful microscopic investigation and the findings compared with the initial gastroscopic diagnoses. As in the work done by Swalm and Morrison, a good correlation was observed in those cases in which definite gastritis by gastroscopy was shown, but a definite lack of correlation was observed in some important instances. As a rule, it is probably safe to conclude that gross gastric changes noted by experienced gastroscopists will be found to correspond fairly closely to histologic changes typical of the various forms of gastritis. It is obvious, however, that minor changes in the gastroscopic picture must be classified with great care, and it is particularly important that such changes are not overemphasized in order to explain symptoms and to form the basis of therapy.

It is still essential to indicate the necessity for continued skepticism in order to arrive at a rational conclusion as to the clinical importance of gastritis as diagnosed by gastroscopy. Howard and Martin [87] stress such a point of view in a careful review of the gastritis problem and refer to Schindler's statement that only about one fifth of the stomachs examined by him are normal, which probably tends to overemphasize greatly the actual incidence of true gastritis. They, like Ruffin and others, correctly urge the accumulation of further data before final conclusions are attempted regarding the incidence or morbidity of various forms of gastritis. They stress the need for adequate gastroscopic studies on psychoneurotic subjects, with or without gastric symptoms. Such a suggestion is of prime importance, and one must again refer to the original observations recorded by Beaumont on the striking changes in the gastric mucosa following emotional upsets and to the recent experiments made by Wolff and Wolf.[2] In my opinion it would seem highly probable that profound and fairly lasting mucosal changes could be observed during acute or more prolonged states of emotional tension which could easily mimic many of the changes now diagnosed as being due to gastritis. Such a concept is stressed, for example, by Kutschera-Aichbergen [88] in an excellent review of the problem. In common with other writers he indicates the important fact that frequently gastroscopic changes are demonstrated which may in no way be associated with

86. Benedict, E. B., and Mallory, T. B.: Correlation of Gastroscopic and Pathologic Findings in Gastritis, read before the Section on Gastro-Enterology and Proctology, American Medical Association, Atlantic City, N. J., June 12, 1942.

87. Howard, J. T., and Martin, L.: The Gastritis Problem, South. M. J. **34**:921, 1941.

88. Kutschera-Aichbergen, H.: Remarks on Gastritis, Wien. klin. Wchnschr. **54**:335, 1941.

clinical symptoms and which, therefore, must be carefully evaluated before initiating an intricate and frequently expensive course of treatment and one which, in addition, may be ill advised.

In an attempt to estimate the symptomatology incident to various forms of gastritis, McClure, Sweetsir and Jankelson [89] make certain interesting points. Of 68 patients showing hypertrophic or atrophic gastritis, in nearly two-fifths the associated symptoms could be attributed to a coexisting ulcer or cholecystic disease. In the remainder mild or severe epigastric discomfort was noted. Unlike the experience recorded by many observers, these authors state that the epigastric pain was invariably related to the time of taking food and was relieved by the ingestion of food or alkali. In the absence of peptic ulcer such a manifestation of symptoms is certainly unusual, to say the least, and is not to be taken as characteristic. The frequent occurrence of fatigue noted by these authors in association with the atrophic type of gastritis is of interest and would certainly raise the suspicion of associated nutritional disturbances, possibly in relation to true deficiency disease.

A further investigation of the significance of achlorhydria with particular reference to gastroscopic observations has been made by Carey and his associates.[90] Although the authors are careful not to draw conclusions, their observations on a large group of patients (233 patients with gastric achlorhydria) are of extreme interest. Perusal of the article would seem to justify the suggestion that the term atrophic gastritis is frequently a misnomer, inasmuch as it implies an inflammatory process rather than a degenerative one or one incident to a generalized deficiency state. In a large number of Carey's patients various manifestations of deficiency disease were carefully noted, and it is highly probable that the gastric changes were simply reflections of a general underlying condition. Extremely careful observations were made on a group of patients with pernicious anemia, and it was noted that the mucosal atrophy was in the body of the stomach and that the antral region was not perceptibly involved. Although the authors state that this is not consistent with Meulengracht's work on the "pyloric gland organ," reference to Fox and Castle's recent article [48] would indicate that not only are the observations entirely correct but they fit in with a proper concept of the expected site of the lesion in pernicious anemia in human beings, Meulengracht's work being based on observations made on the hog stomach. These authors, in company with others already cited, feel that the subject of gastritis has to be further investigated to obtain a com-

89. McClure, C. W.; Sweetsir, F. N., and Jankelson, I. R.: Chronic Gastritis: Gastroscopic and Clinical Study, New England J. Med. **225**:259, 1941.

90. Carey, J. B.; Wetherby, M., and Ylvisaker, R. S.: Gastric Observations in Achlorhydria, Am. J. Digest. Dis. **8**:401, 1941.

plete correlation between gastroscopic data, histologic data on resected or biopsy material and clinical evidence of disease.

The role of chronic alcoholism in the production of chronic gastritis is still in the realm of speculation. As Berry [91] points out, evidence from the literature on attempts to produce chronic alcoholic gastritis is inconclusive. Pathologists have not supplied any evidence in the literature of unequivocal chronic gastritis due to alcohol. Berry cites one well controlled observation made by Hirsch in 1916 who demonstrated frequent gross and microscopic petechiae or ecchymotic hemorrhages but no true inflammatory reaction. No previous gastroscopic study of alcoholic addicts has appeared in the American literature. In the author's opinion, in the one report in the foreign literature, on 45 patients, the extensive atrophic gastritis described was probably not due to alcohol directly. Berry carried out gastroscopic studies on 100 patients with unquestionable chronic alcoholism. All were ambulatory, and none had an enlarged or painful liver or ascites. Sixteen came to the clinic because of some type of digestive distress, while the remaining 84 did not seek medical help but were induced to come to the clinic for this study. In this group of patients, one-third showed no evidence of gastritis, a second third showed mild chronic superficial gastritis and a final third showed unequivocal chronic gastritis. These observations are timely and certainly present substantial evidence that chronic alcoholism may be associated with chronic inflammatory changes in the gastric mucosa. Although the observations are of extreme interest, they still fail to prove the point, however, as to the cause of the condition. It may well be that, as in cirrhosis, one must carefully differentiate between cause and associated factors. It is entirely within the realm of possibility that in persons chronically addicted to alcohol, changes in the gastric mucosa develop partly because of the stimulating or irritating effect of alcohol and partly because of associated dietary indiscretions, or more probably, deficiencies based on the substitution of alcohol for food. The subject is still *sub judice* and will warrant further careful observations. In spite of failure to present absolute proof of the etiologic role played by alcohol in the production of chronic gastritis, there can be little doubt from these observations and clinical experiences that chronic addiction to alcohol carries in its train serious consequences, among which is the frequent occurrence of chronic gastric disease. An entirely comparable report on an equal number of subjects is presented by Gray and

91. Berry, L. H.: Chronic Alcoholic Gastritis: Evaluation of the Concept, with Gastroscopic Studies in One Hundred Cases, J. A. M. A. **117**:2233 (Dec. 27) 1941.

Schindler.[92] The 100 men who were examined had consumed an average of 2.8 pints (1.3 liters) of alcohol daily for more than twenty years, yet gastroscopic examination revealed that approximately half the subjects did not give evidence of any important gastric abnormalities. In 45 per cent the gastric alterations consisted merely in superficial gastritis, atrophic gastritis or a combination of the two. Gastrointestinal complaints occurred in about two thirds of those showing severe grades of gastritis, whereas only 7 per cent of the addicts with normal-appearing stomachs experienced "indigestion." No correlation was observed between the incidence and severity of gastritis and the duration of alcoholism, the amount of alcohol consumed, the abuse of nicotine, dental infection or vitamin deficiencies. It is obvious that the question is still open.

Certain unusual gastroscopic observations are worthy of mention. Einsel [93] reports a case of superficial ulcerative gastritis following heavy antisyphilitic therapy. Because of gastric distress and nausea tryparsamide treatment was stopped, and two weeks later roentgen and gastroscopic examination showed superficial erosions of the gastric mucosa. Seven months later a second gastroscopic examination revealed that the gastric mucosa was entirely normal, except for some possible transient changes secondary to the recent administration of acetylsalicylic acid.

It is not surprising that advanced pulmonary tuberculosis may be associated with various gastrointestinal abnormalities. Hardt and his associates [94] made a gastroscopic study of 150 patients with late pulmonary disease due to tubercle bacilli. Approximately one-third showed atrophic changes similar to those classified as atrophic gastritis, and in addition, at times there was a coincidence of superficial lesions with marked hyperemia and mucosal edema, as well as evidence of local atrophy. The authors conclude, probably correctly, that the hyperemic, edematous stage represents an earlier lesion. In all probability, the gastritis is nonspecific as far as tuberculosis is concerned, but it is unfortunate that no associated histologic studies were performed.

That gastritis alone may be the sole cause of serious or even fatal hemorrhage is now firmly established. A further report on this particular aspect of the problem of gastritis is presented by Benedict.[95] It

92. Gray, S., and Schindler, R.: The Gastric Mucosa of Chronic Alcoholic Addicts: A Gastroscopic Study, J. A. M. A. **117**:1005 (Sept. 20) 1941.

93. Einsel, I. H.: Superficial Ulcerative Gastritis Following Triparsamide Therapy for Syphilis, Am. J. Digest. Dis. **9**:191, 1942.

94. Hardt, L. L.; Weisman, M., and Coulter, J. S.: Gastric Atrophy in Advanced Pulmonary Tuberculosis, Proc. Inst. Med. Chicago **13**:418, 1941.

95. Benedict, E. B.: Hemorrhage from Gastritis: A Report Based on Pathological, Clinical, Roentgenological and Gastroscopic Findings, Am. J. Roentgenol. **47**:254, 1942.

includes proof from autopsy and from surgical material, as well as from numerous gastroscopies, in over 200 cases of gastritis studied during a particular period. Bleeding occurred in one fifth of the cases, irrespective of the type of gastritis. Study of an additional group of cases of ulcer yielded data in keeping with those presented by other observers, that at times gross hemorrhage may occur from the associated gastritis rather than from the local ulcer. It is of interest that careful roentgen examination suggested gastritis in only 20 per cent of the cases in which gross hemorrhage was due to gastritis alone.

The cause for the divergence between the roentgen and the gastroscopic diagnosis of gastritis is well expressed by Berridge.[96] He rightly points out that the roentgenologist examines the gastric mucosa in a definite state, that of resting relief, whereas the gastroscopist employs an inconstant amount of distention. The article bears the imprint of a certain amount of defense reaction but is nevertheless of interest. The supplementary roles of the roentgenologist and the gastroscopist are well outlined by Davidson and Rose,[97] who compare the respective data from 600 gastroscopic investigations, 226 of which were checked by roentgen examination. According to these authors, roentgen investigation may give more information than gastroscopy in the following conditions: lesions on the lesser curvature of the pyloric antrum; estimation of the size of an antral cancer; lesions on the greater curvature, and lesions in the distal pouch of an hourglass stomach. Per contra, they point out that the early and accurate recognition of primary neoplasm in gastric ulcer belongs to the field of gastroscopy. Such an article is reasonably critical of the two fields of investigation and provides a basis for adequate and advantageous cooperation between the services involved.

It is still unfortunately true that adequate gastroscopic examination is frequently missing in cases in which the presence of a neoplastic lesion of the stomach has been suspected but not proved by roentgen examination. This is well illustrated in an article by Myhre,[98] who presents an adequate description of the significance of large niches in the stomach. In 23 instances surgical exploration had followed the roentgen examination, but it is of interest to note that of the large craters encountered in the 23 patients, only 9 were due to carcinoma and the other 14 were associated with benign ulcers. The average diameter of the benign niches was around 4 cm., in 1 individual case an ulcer crater 6.5 cm. in diameter

96. Berridge, F. R.: The Radiological Aspects of Gastritis, Brit. J. Radiol. **15**:1, 1942.

97. Davidson, S. W., and Rose, J. D.: The Value of Cooperation Between the Radiologist and the Gastroscopist, Brit. J. Radiol. **14**:307, 1941.

98. Myhre, H.: Significance of Large Niches in Stomach, Acta radiol. **22**:482, 1941.

being noted. Those patients with malignant disease did not show any greater size of the craters. Such findings are important in demonstrating the need for accurate examination by an experienced gastroscopist as a supplement to careful roentgen study. There is little doubt that many of these operations could have been properly avoided and the gastric lesions permitted to heal under medical therapy had gastroscopy been performed. Obviously, the gastroscopist cannot always be the final arbiter in this difficult question, but in most instances, repeated careful observations will provide the necessary information in differentiating between a benign and a malignant lesion.

Schindler [99] contributes another careful series of observations on the appearance of the gastric mucosa in the presence of benign adenomas of the stomach. Thirty-six adenomatous polyps were observed in the course of 2,167 consecutive gastroscopies. The finding of associated atrophic gastritis occurred with sufficient frequency to lead him to the conclusion that an atrophic gastric mucosa has a seven times greater predisposition to the formation of such tumors than has a normal gastric mucosa. Here again, such a definite statement must be scrutinized rather carefully in the light of subsequent examinations, but the observation is important and cannot be dismissed.

The rarity of multiple polyps of the stomach is evidenced in a report by Giere.[100] In a review of over 34,000 autopsies at the University of Minnesota only 32 instances were encountered. He cites Stewart as reporting only 20 cases of multiple polyps in 11,000 autopsies, at the Leeds General Infirmary, and Carmen as encountering only 2 instances in 50,000 roentgen examinations of the stomach. The author reports 1 case, which again illustrates the importance of the correlation between gastroscopic and roentgen examination. In this particular case gastroscopy confirmed the roentgen evidence of polyps but gave additional information in that it disclosed the presence of polyps not seen on roentgen examination, as well as erosions and evidence of atrophic gastritis.

A rather interesting study is that made by Usher,[101] who reports gastroscopic observations on 19 patients suffering from varying degrees of rosacea, with control studies on 15 patients with other types of dermatoses. Gastritis of varying degrees of severity was present in all except 1 of the patients with rosacea, while of the patients with dermatoses of

99. Schindler, R.: The Gastric Mucosa in Benign Adenomas, Am. J. Digest. Dis. **9**:149, 1942.

100. Giere, C. N.: Gastric Polyposis: Case Observed Gastroscopically, South. M. J. **34**:927, 1941.

101. Usher, B.: Gastroscopic Observations in Rosacea, Arch. Dermat. & Syph. **44**:251 (Aug.) 1941.

varying types, only 4 showed any evidence of gastric alterations. No constant type of gastritis was noted in the patients with rosacea. Repeated gastroscopic investigations in 2 patients during the course of treatment showed coincidental improvement both in the gastritis and in the rosacea, which is further evidence of the probable influence of deficiency conditions in causing gross gastric abnormalities.

To those actually performing gastroscopies a modification of the Wolff-Schindler gastroscope reported by Taylor [102] may be of interest. One possible advantage of the instrument described is that the flexibility is controlled and, if desired, the instrument can be made completely flaccid.

The report by Schiff and Shapiro [103] on perforation of the stomach during the use of the flexible gastroscope is important for two reasons: First, it illustrates the potential hazard attaching to the use of the gastroscope, and second, it emphasizes the extreme infrequency with which such accidents occur. It is important to note that there was no pain at the actual time of perforation, but the appearance of blood covering the instrument at once suggested what had occurred, and the subsequent appearance of abdominal "spasms" led to a correct diagnosis. Schindler has previously pointed out that the diagnosis of perforation of the stomach at gastroscopy may be made prior to the onset of pain if the stomach remains collapsed in spite of air inflation. A still more unusual accident secondary to gastroscopy is that described by Touroff,[104] who reports a perforation of the cervical portion of the esophagus, due apparently to the dislodging of the flexible rubber bougie at the distal end of the apparatus. In this instance, the appearance of a small amount of blood in the patient's mouth caused withdrawal of the instrument, which had been passed only about 6 inches (15 cm.) beyond the upper incisors, and it was noted on withdrawal that the rubber bougie was missing. Within a few minutes the patient complained of pain over the right side of the neck, and subsequent examination at operation revealed perforation of the esophagus and the foreign body lying free in the periesophageal tissue. Prompt operation resulted in a perfect recovery. Although the possibility of such serious accidents should not be overlooked, their rarity is disclosed in the results of a recent questionnaire circulated by Schindler (1940), which showed that only 10 serious accidents had occurred in a total of over 22,000 gastroscopic examinations.

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102. Taylor, H.: A New Gastroscope with Controllable Flexibility, Lancet **2**:276, 1941.

103. Schiff, L., and Shapiro, N.: Perforation of the Stomach with the Flexible Gastroscope: Case Report, Am. J. Digest. Dis. **8**:260, 1941.

104. Touroff, A. S. W.: Perforation of the Cervical Esophagus with the Flexible Gastroscope, Ann. Surg. **114**:369, 1941.

Peptic Ulcer.—The ulcer problem continues to attract a proper amount of attention, both from the experimental side and from various therapeutic angles. Among other researches attempting to throw light on the causation of this troublesome condition the work of Necheles and Olson [105] should be mentioned. These authors carried out an experimental investigation of gastrointestinal secretions and motility following burns and their relation to ulcer. The results of severe burns were studied in a series of dogs under anesthesia. Salivary, biliary and pancreatic secretions were practically always diminished. In general, the volume of gastric secretion and the degree of acidity increased, and in 1 animal studied a prepyloric ulcer was encountered. The increased volume of gastric secretion seemed to depend in part on infusions, and the increased acidity appeared to be related to the effect of infusions plus previous feeding. After peripheral burns a considerable increase in intra-abdominal pressure and gastric motility was observed. The change in gastric motility was particularly marked in the pyloric antrum and began immediately after a burn had been produced. This increase in motor activity was not altered by bilateral section of the splanchnic nerves or of the vagi or of both. In fact, vagal section seemed to enhance the gastric motor response to a burn, but the intravenous injection of atropine abolished the hypermotility. The relation of these results to Curling's ulcer are fully discussed by the authors, who undoubtedly have contributed some important information to the causation of at least one type of peptic ulcer.

The effect of local vascular changes in the stomach and the duodenum in relation to the ulcer problem has been approached by Berg,[106] who in normal and in vagotomized dogs was able to produce motor abnormalities and scattered superficial gastric erosions after a single injection of pitressin. With frequent injections gastric lesions were induced in normal and in vagotomized animals, particularly in the latter. The lesions were extensive, and acute and hemorrhagic duodenitis was also encountered. In sympathectomized animals gastric lesions were not obtained. Microscopically, some of the ulcerated areas extended down to the muscularis. The performance of vagotomy and sympathectomy without the use of pitressin did not result in ulcerating lesions. The relation between such results and peptic ulcer in human beings is, of course, inferential, but there can be no doubt that various factors which

105. Necheles, H., and Olson, W. H.: Experimental Investigation of Gastrointestinal Secretions and Motility Following Burns and Their Relation to Ulcer, Surgery **11**:751, 1942.

106. Berg, M.: Experimental Peptic Ulcerations by Vasomotor Episodes (Pitressin Episodes) and Autonomic Disturbances, Arch. Path. **33**:636 (May) 1942.

in human beings produce transient or prolonged alterations in the muscular and the vascular activity of the stomach may well underlie the production and recurrence of peptic ulcer. It is highly probable that numerous factors play a role, including those that are neurogenic or hormonal in origin.

In observations on cinchophen ulcer produced in dogs Slutzky, Wilhelmj and Stoner [107] administered chorionic gonadotropin and posterior pituitary extract to two separate groups of animals. All the animals died from perforation of the ulcer resulting in peritonitis. There was no evidence of healing. It is of interest, however, that those animals treated with posterior pituitary extract revealed a marked inhibition of gastric acid secretion. These animals probably survived somewhat longer than the others, but the action of the pituitary extract did not prevent the occurrence of gastric ulceration and was probably an indirect action secondary to vasoconstriction.

The contribution of gastric acid to the formation of ulcer in the jejunum and the duodenum has long been recognized, although the exact mode of its activity is still not fully understood. Schiffrin and Warren [108] obtained what would seem to be an entirely logical series of results in cats in which various segments of the small bowel were perfused with solutions of hydrochloric acid alone and hydrochloric acid combined with pepsin. Severe ulceration resulted, and it was found that the threshold of peptic activity necessary for ulceration of the jejunum was within the range of that in normal canine gastric juice. Maximum ulceration occurred with pepsin when it was employed in a medium having a p_H within the optimum range for peptic digestion. The experiments throw no light on whether the proteolytic activity of gastric juice is an etiologic factor or an accessory factor in the production of peptic ulcer in human beings.

Recent advances in knowledge of the hormonal control of gastric secretion have already been discussed. The possible therapeutic value of a gastric secretory depressant occurring in the urine of certain persons has been studied by Sandweiss and his collaborators.[109] The urine of pregnant women and of normal nonpregnant women has been found to contain a principle capable of benefiting Mann-Williamson ulcers in dogs.

107. Slutzky, B.; Wilhelmj, C. M., and Stoner, M.: The Effect of Antuitrin-S and Posterior Pituitary Extract on Cinchophen Ulcer in Dogs, Am. J. Digest. Dis. **8**:469, 1941.

108. Schiffrin, M. J., and Warren, A. A.: Some Factors Concerned in the Production of Experimental Ulceration of the Gastro-Intestinal Tract in Cats, Am. J. Digest. Dis. **9**:205, 1942.

109. Sandweiss, D. J.; Sugarman, M. H.; Friedman, M. H. F.; Saltzstein, H. C., and Farbman, A. A.: The Effect of Urine Extract on Peptic Ulcer: An Experimental and Clinical Study, Am. J. Digest. Dis. **8**:371, 1941.

Experiments with extracts derived from the urine of normal men are incomplete. The urine of patients with ulcer contains much less of this inhibitory principle, and when an extract was administered in small doses, as has been already noted in animals, it produced a negligible inhibitory effect on gastric secretion, but in Mann-Williamson dogs it appeared to influence healing in some manner through stimulation of fibroblastic and epithelial proliferation and the formation of new blood vessels. With the extract at present available, it was found that when small doses were given intravenously or large doses administered subcutaneously, inhibition of gastric secretion was obtained. Sandweiss has demonstrated that subcutaneous injection of large doses of urine extract in patients with duodenal ulcer tends to inhibit the volume of gastric secretion and the total output of free acid after stimulation with histamine. The concentration of free acid was unaffected. Although the author hesitates to draw premature conclusions, it appears from the studies that urine extract therapy gave encouraging results in a series of 63 patients with chronic duodenal ulcer. It did not prevent recurrences, but he felt that a higher percentage of remissions resulted during treatment with the urine extract than was obtained with the usual dietary regimens or with other parenterally administered products. As has been evident in all his previous publications, Sandweiss is extremely conservative in attempting to evaluate the results of parenteral therapy, but from his observations it would seem reasonable to hope that a combination of the usual orthodox therapeutic measures plus urine extract therapy may produce more encouraging and more lasting results in the treatment of peptic ulcer.

Indirect evidence of an altered response in patients with ulcer to the normal inhibition of gastric acidity following the entrance of acid chyme into the duodenum is obtained from the studies of Shay and his collaborators.[110] In normal persons they demonstrated a depression of gastric acid secretion following the instillation into the duodenum of optimal amounts of free hydrochloric acid. Similar studies carried out in patients with duodenal ulcer after the intraduodenal instillation of even greater amounts of acid failed to elicit a normal inhibitory response in regard to gastric secretion. Such results would seem to be additional confirmation of the mode of action of enterogastrone or some similar substance.

An interesting note on the incidence of peptic ulceration is to be found in the report by Gordon and Manning,[111] who examined the

110. Shay, H.; Gershon-Cohen, J.; Fels, S. S., and Siplet, H.: A Self-Regulatory Duodenal Mechanism for Gastric Acid Control and an Explanation for the Pathologic Gastric Physiology in Uncomplicated Duodenal Ulcer, Am. J. Digest. Dis. **9**:124, 1942.

111. Gordon, J. S., Jr., and Manning, J. J.: An Autopsy Survey of Gastro-Duodenal Ulcers in Philadelphia General Hospital 1920-1937, Am. J. M. Sc. **202**:423, 1941.

results of nearly 30,000 autopsies performed in the Philadelphia General Hospital over a seventeen year period. In this series peptic ulceration was encountered in 548 autopsies or 2.75 per cent, with no racial difference in incidence between white persons and Negroes. Males showed ulcerations only twice as frequently as females. Peaks in the incidence of the lesions appeared to be in the fifth and the seventh decade. Such a finding is of interest, though taken by itself it is difficult to interpret, inasmuch as it may not reflect the clinical incidence of ulcer in living patients. For comparative purposes the report by McMullen [112] should be added. Of a total of 4,400 patients subjected to roentgen examination of the gastrointestinal tract, 20 per cent were found to have peptic ulcer. As might have been predicted, duodenal ulcer occurred about four times as often as gastric ulcer and was slightly more common in men than in women. In this group of patients the peaks of incidence of gastric and of duodenal ulcer among women occurred in the fifth and the fourth decade, respectively, and similarly, the greatest incidence of gastric and of duodenal ulcer among men occurred in the sixth and the fifth decade, respectively.

Duodenal ulcer in children is undoubtedly overlooked because of its infrequent occurrence. A relatively small number of authenticated cases of ulcer in the early years of life have been reported in the literature. In recent years the diagnosis has been somewhat more frequently established, and the report of Willingham [113] is worthy of comment. In this instance, duodenal ulcer was eventually recognized in a 6 year old boy, for whom this diagnosis had not been considered until he vomited blood. The author correctly points out the need for more careful roentgen investigation of gastrointestinal complaints in children. Bird, Limper and Mayer [114] in a review of the literature noted 118 cases in which operations were performed for peptic ulceration in infants and children. They report 1 case in which operation was performed within thirty-four and a half hours after birth for a perforated duodenal ulcer, with a satisfactory outcome.

Because of the frequency with which digestive symptoms occur in the presence of heart disease, Walsh and his collaborators [115] made a statis-

112. McMullen, J. W.: A Roentgenographic Study of the Relative Incidence of Gastric and Duodenal Ulcer, Radiology **37**:194, 1941.

113. Willingham, T. I.: Duodenal Ulcer in Children: Report of Case, J. M. A. Georgia **30**:271, 1941.

114. Bird, C. E.; Limper, M. A., and Mayer, J. M.: Surgery in Peptic Ulceration of Stomach and Duodenum in Infants and Children, Ann. Surg. **114**: 526, 1941.

115. Walsh, B. J.; Bland, E. F.; Taquini, A. C., and White, P. D.: Association of Gallbladder Disease and of Peptic Ulcer with Coronary Disease, Am. Heart J. **21**:689, 1941.

tical study of the necropsy protocols of a large group of patients who died at the age of 20 or more years. Of 2,737 patients, nearly one fifth had atherosclerosis of the coronary vessels and one sixth of the entire group showed structurally abnormal gallbladders. There were 122 instances of coronary disease and disease of the gallbladder occurring in the same person. Peptic ulceration was encountered in a little over 5 per cent of patients. It was evident from the protocols that disease of the gallbladder occurred almost twice as often in patients with coronary disease as in those with normal coronary arteries, but there was no evidence of any similar association between arterial disease and peptic ulceration. The last-named association is probably coincidental. In this connection a comment is warranted on the report by Hochrein and Schleicher,[116] who believe that there is a close relation between peptic ulcer and coronary insufficiency. These authors have attempted to prove their point on the basis of clinical impressions and electrocardiographic studies on 100 patients with ulcer and with or without symptoms of cardiac disease. The studies are far from convincing, however, and are not borne out by the statistical data presented in the preceding paper. Neurocirculatory disturbances are certainly not uncommon in patients with ulcer, and it should be pointed out at the same time that by far the great majority of patients with ulcer have a tendency toward hypotension, rather than hypertension, and in my opinion, have relatively few symptoms suggestive of coronary heart disease. Hochrein and Schleicher illustrate their point by referring to the gastrocardiac disturbances frequently associated with hiatus hernia, a condition in no way comparable to ulcer inasmuch as it occurs in an entirely different type of person, in whom cholelithiasis and changes in the coronary arteries are common. The article is quite unconvincing but is of interest because of the questions that it raises, particularly in relation to the similarity between symptoms arising from cardiovascular disease and those due to disturbances in the digestive tract.

It has previously been pointed out (Blackford and others) that atypical histories of ulcer occur with sufficient frequency to warrant serious consideration in cases of doubtful disease of the digestive tract. Of equal importance is the fact that occasionally patients with ulcer may have absolutely no symptoms until serious accidents occur, such as perforation or hemorrhage. Norfleet [117] comments on such an occurrence, citing individual cases, and in this regard it is pertinent to mention that

116. Hochrein, M., and Schleicher, I.: Peptic Ulcer and Angina Pectoris, München. med. Wchnschr. **88**:328, 1941.

117. Norfleet, W. J.: Peptic Ulcers, with Special Reference to Non-Symptomatic Type and Case Reports of Rupture into Peritoneal Cavity and Intestinal Hemorrhage, New Orleans M. & S. J. **94**:183, 1941.

evidence is accumulating that a higher threshold of pain may be a not uncommon phenomenon in patients with ulcer. A duodenal ulcer, for example, may be activated and may progress rapidly without the patient being aware of painful or uncomfortable sensations, thereby clouding the diagnosis or postponing a diagnosis until a serious complication occurs.

Therapeutic measures directed toward the healing of ulcer present little modification over those noted in previous years, except for the as yet untried benefits of preparations of urogastrone or enterogastrone. Antacid therapy still occupies an important place in the literature, and it is of interest to note the insistence on the various means of obtaining control of gastric hyperacidity that are still advocated. Smith,[118] for example, believes that continuous intragastric drip provides the only means of constantly maintaining a low acid level with the use of milk and (or) aluminum hydroxide. The mechanical difficulties encountered in the use of aluminum hydroxide drip therapy are noted by Drumheller,[119] who has devised a rather complicated mechanical means of insuring a constant steady flow of this bland material. The principles of tube therapy are far from new, although the material introduced into the drip apparatus have been modified from time to time. Secher [120] is another warm advocate of an inlying tube for the treatment of peptic ulcer, using a mixture of various bland foods to maintain a good state of nutrition. The results, however, would seem to be no better than those obtained by simpler methods, and it would seem that in many instances the annoyance of an inlying tube could be avoided without prolongation of the hospital stay for patients with ulcer or without unsatisfactory end results as far as healing is concerned. It would seem that the indications for tube therapy are few and that it should be employed only in selected cases in which other simpler methods have failed to be effective.

Compounds containing bismuth have been used intermittently for years in the treatment of gastric disease, and the report of Alstead [121] is therefore of interest. He believes that in therapeutic doses bismuth carbonate offers little protection to the gastric mucosa and frequently tends to collect in dependent portions without actually protecting the ulcerating areas. He concludes that in gastrointestinal disease bismuth carbonate is no more valuable than powdered milk or lactose in the relief of pain.

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118. Smith, W. E.: The Control of Gastric Hyperacidity in Peptic Ulcer, Brit. M. J. **2**:13, 1941.

119. Drumheller, G. H.: Problems Encountered in the Use of Aluminum Hydroxide Gel by Naso-Gastric Drip in the Treatment of Peptic Ulcer, Am. J. Digest. Dis. **8**:443, 1941.

120. Secher, K.: Tube Treatment of Chronic Gastric and Duodenal Ulcers, Acta med. Scandinav. **106**:1, 1941.

121. Alstead, S.: Action of Bismuth Carbonate in Gastric Disease, Lancet **2**:420, 1941.

The troubled question of alkalosis complicating alkali therapy of peptic ulcer is thoroughly studied by Kirsner and Palmer,[122] who are consistent and enthusiastic advocates of this form of therapy. The occurrence of alkalosis on one or more occasions in 111 patients with peptic ulcer treated by the Sippy regimen is carefully analyzed, and the symptomatology and chemical changes noted. Alkalosis was not a direct function of the quantity of alkali received, and there was no constant relation between the severity of symptoms and the degree of chemical alkalosis. It is of some interest that bleeding occurred in 60 of 135 episodes of alkalosis, but there seemed to be no correlation between the frequency of alkalosis and the severity of the bleeding. Such a high frequency of hemorrhage in alkalotic episodes suggests the possibility that sudden massive loss of blood may be associated with an alteration in renal blood flow sufficient to be an important factor in the production of alkalosis. Disease of the genitourinary tract was demonstrated in only 16 patients. Another precipitating factor suggested by the authors was excessive loss of gastric juice, either by vomiting or by therapeutic aspiration. The important fact is noted that it was not necessary to discontinue alkali therapy or to administer additional chloride in 51 of the 135 episodes. In the remaining episodes, however, treatment was modified by a change in the antacid employed, by discontinuance of the alkali or by parenteral administration of fluids and sodium chloride. The effect of prolonged alkali therapy on renal function was studied in half the patients, and it was observed that renal function was not permanently decreased by prolonged administration of alkali. Such a study is of value because of the completeness with which this particular phase of antacid therapy is reviewed. Whether antacids are necessary in the successful handling of most peptic ulcers is still a matter of individual experience and opinion, although there can be no doubt that such treatment represents a valuable and most important contribution to the effective management of many ulcer problems. The successful treatment of peptic ulcer without alkalis is discussed by Dick and Eisele,[123] who report their experiences in the treatment of patients with ulcer by simply dietary measures. Such a report contributes nothing new but is of importance because it indicates the efficacy of the simplest method of treatment and one which is so frequently successful in dealing with this condition.

The diagnosis of bleeding from peptic ulcer is frequently missed because of failure to perform simple stool examinations. It is of importance to note that a daily loss of blood from the upper portion of the intestinal tract of as little as approximately 10 cc. may result in positive

122. Kirsner, J. B., and Palmer, W. L.: Alkalosis Complicating the Sippy Treatment of Peptic Ulcer, Arch. Int. Med. **69**:789 (May) 1942.

123. Dick, G. F., and Eisele, C. W.: The Treatment of Peptic Ulcer Without Alkalis, J. A. M. A. **118**:38 (Jan. 3) 1942.

results of tests for occult blood in the stool in over 40 per cent of cases. Such results were obtained by Kirschen and associates [124] in studying 146 normal persons to whom small divided doses of hemoglobin were administered and whose stools were tested by the routine benzidine slide test. The delicacy of this test is such that unless patients are maintained on strictly meat-free diets, it is doubtful whether a barely positive result is of significance, and great care should be used in the interpretation of such minimal findings. The authors contribute one point of incidental interest, namely, that carmine per se when used for the marking of stools may yield a positive result in a test for blood in the feces. A continuation of previous careful studies on the significance of blood in the stools is reported by Schiff and his collaborators.[125] Observations were made on a group of subjects after the introduction of varying quantities of whole blood into the stomach, and the results of stool examinations were recorded. Tarry stools were obtained in subjects given amounts of blood as small as 200 cc. It was shown that stools may be entirely bloody and never tarry as a result of intestinal hypermotility. Such a confirmation of a clinical fact is reassuring and suggests that a grossly bloody stool does not necessarily indicate hemorrhage from the small intestine or the colon. The number of bloody or tarry stools is not directly related to the amount of blood in the stomach. One patient had five bloody stools after the introduction of 1,000 cc. of blood, whereas another had but three tarry stools after a similar introduction of 2,000 cc. of blood. Bloody stools may be passed for as long as three days and tarry stools for as long as five days after intragastric administration of a single quantity of blood. Positive results of guaiac tests for occult blood in the stools may persist for as long as ten days after the ingestion of 250 cc. of blood. The conclusions, although not new, should be stressed because of their clinical application. From the results of the experiments Schiff and his associates believe that the passage of a tarry stool does not necessarily indicate the occurrence of a severe hemorrhage into the digestive tract and that the persistence of tarry stools or of occult blood in the stools does not necessarily indicate the continuation of such a hemorrhage.

Gross hemorrhage unassociated with pain may be and frequently is encountered in the presence of a peptic ulcer, and as has previously been noted, an elevated individual threshold for pain may explain many of these occurrences. That other causes may be responsible for painless gross bleeding from the stomach or the duodenum is shown in the short

124. Kirschen, M.; Sorter, H., and Necheles, H.: Occult Blood, with a Note on the Use of Carmine for the Marking of Stools, Am. J. Digest. Dis. **9**:154, 1942.

125. Schiff, L.; Stevens, R. J., Shapiro, N., and Goodman, S.: Observations on the Oral Administration of Citrated Blood in Man: II. The Effect on the Stools, Am. J. M. Sc. **203**:409, 1942.

report of Moschcowitz, Mage and Kugel.[126] Of 14 patients who came to necropsy in association with massive gastroduodenal hemorrhage without pain, only 3 had gastrointestinal bleeding from a chronic peptic ulcer. In the other 11 cases there were associated conditions that might be classified as gastritis or as being secondary to more superficial lesions of varied natures. It is quite possible that the superficiality of the lesions in erosions causing even fatal hemorrhage may serve in part as an explanation for the absence of pain.

The therapy of bleeding ulcers is still a matter of choice, if one can judge by the varied results reported in the literature. Nicholson and Miller,[127] in a careful analysis of therapeutic results, express the belief that a prompt feeding program following hematemesis plus administration of a reasonable amount of fluid gives far better results than any other type of treatment. They believe that the type of diet is of secondary importance to the requirement that food be given promptly, irrespective of the degree of bleeding, frequently and in adequate amounts. Their observers also feel strongly that the use of morphine should be strictly avoided because of its effect on the tonicity of the duodenal musculature. They believe that the prompt feeding program is effective probably because it meets nutritional demands; supplies fluid to counteract shock; neutralizes the gastric acidity, thus preventing further erosion in the ulcerated areas, and increases intragastric and intraduodenal pressure, thus tending to close the open and bleeding vessel. Although the mortality figures vary, other authors, such as Eichhorn,[128] Chaikin and Tannenbaum[129] and MacMillan,[130] report similar beneficial results. Eichhorn carried out comparative studies on a series of 81 patients with bleeding ulcers. Thirty-three patients were treated by initial starvation, and the remainder (38) were fed immediately. There were no deaths in the second group of patients, whereas in those treated by initial starvation, there was a mortality of 19 per cent. Eichhorn believes that the principle involved in the Meulengracht regimen greatly lowers the mortality rate, provides more comfort for the patient and results in a shorter stay in the hospital, a statement that is borne out by the results

126. Moschcowitz, E.; Mage, S., and Kugel, V. H.: Causes of Painless Gastro-Duodenal Hemorrhage, Am. J. M. Sc. **202**:48, 1941.

127. Nicholson, J. T. L., and Miller, T. G.: The Prompt Feeding Program for Bleeding Gastric and Duodenal Ulcer: A Report on Thirty-Two Cases and an Analysis of 1396 Recorded Cases, Am. J. Digest. Dis. **8**:446, 1941.

128. Eichhorn, J. P.: Immediate Feeding Versus Initial Starvation in the Treatment of Bleeding Peptic Ulcer, Am. J. M. Sc. **203**:428, 1942.

129. Chaikin, N. W., and Tannenbaum, O.: Bleeding Peptic Ulcer: A Clinical Study with Special Reference to the Meulengracht Regimen, Am. J. Digest. Dis. **9**:150, 1942.

130. MacMillan, R. L.: Massive Hemorrhage from Stomach: Its Diagnosis and Treatment, North Carolina M. J. **2**:476, 1941.

of a more or less similar study by Chaikin and Tannenbaum. Rafsky and Weingarten,[131] on the contrary, state that the mortality rate in a group of patients treated by restricted dietary measures is essentially no different from that in a group treated by the Meulengracht diet. These authors prefer their own method of treatment, which involved starvation for the first day after admission to the hospital, or longer if bleeding continues, following which hourly feedings of cereal or milk were administered, together with the usual supportive measures employed by most physicians. Intraduodenal feeding was employed from the fourth to the seventh day after admission in the presence of pain. Emery,[132] by comparing the results of treating 36 patients with bleeding ulcer by the Meulengracht regimen with the results obtained on a group of 50 patients treated previously by the Sippy regimen, believes that there was no essential difference in the mortality figures. He states that there was no evidence that bleeding stopped any more rapidly on the Meulengracht than on the Sippy regimen, although the former was undoubtedly pleasanter for the patient. In most instances, it can be safely asserted, however, that the principle of early feeding after hemorrhage is to be desired and that in some form or another it constitutes the method of choice, as was indicated some years ago by Andresen. The question of iron therapy in the treatment of the anemia due to gastrointestinal bleeding has always occasioned a certain amount of controversy because of the possible irritative action of iron salts. Ehrenfeld and Wallace [133] believe that colloidal iron hydroxide in combination with aluminum hydroxide may be given continuously without causing any gastric irritation to patients with peptic ulcer and that in those patients with persistent chronic bleeding of a mild character it is possible to maintain a constant red cell count and hemoglobin level by such means.

Schiff and associates [134] continue to stress the prognostic significance of the rise in blood urea nitrogen following hematemesis or melena. Chunn, Harkins and Boals [135] similarly mention the prognostic importance of blood urea determinations in cases of massive bleeding from the upper portion of the gastrointestinal tract. The latter authors, however,

131. Rafsky, H. A., and Weingarten, M.: Bleeding Peptic Ulcer: Clinical Appraisal of Various Methods of Treatment Based on a Series of Four Hundred and Eight Cases, J. A. M. A. **118**:5 (Jan. 3) 1942.

132. Emery, E. S., Jr.: A Comparison of the Meulengracht and Sippy Therapies in the Care of Bleeding Peptic Ulcers, Am. J. Digest. Dis. **8**:387, 1941.

133. Ehrenfeld, I., and Wallace, R. P.: Iron as a Therapeutic Supplement in Peptic Ulcer Therapy, Am. J. Surg. **53**:470, 1941.

134. Schiff, L.; Stevens, R. J.; Moss, H. K., and Garber, E. S.: The Prognostic Significance of the Blood Urea Nitrogen Following Hematemesis or Melena, Am. J. Digest. Dis. **9**:110, 1942.

135. Chunn, C. F.; Harkins, H. N., and Boals, R. T.: Alimentary Azotemia and the Bleeding Peptic Ulcer Syndrome, Arch. Surg. **43**:773 (Nov.) 1941.

mention in their article the results of animal experiments in which roentgen nephritis was produced by the method of Hartman. In these animals the administration of blood by stomach tube produced much more prolonged azotemia than that resulting in control animals. Such a finding would seem to confirm the careful observations previously reported by Johnson, who indicated that the degree of azotemia was more dependent on the renal factor than on any others and was of little, if any, prognostic significance. Black [136] stresses the importance of alteration in renal function as a significant factor in the production of azotemia secondary to gastrointestinal hemorrhage, and in addition, presents observations showing that a marked rise in the blood level of amino acid nitrogen occurs at the same time. He suggests that the increase in amino acid nitrogen probably indicates temporary hepatic dysfunction. A general discussion of the biochemical changes associated with hemorrhage from the stomach and the duodenum and a consideration of the necessity of therapeutic measures directed toward an improvement in the urinary excretion of urea is to be found in an article by Bick and Wood.[137]

Possible transient myocardial changes secondary to massive hemorrhage from peptic ulcer are reported by Scherf and his collaborators.[138] Conclusions as to such myocardial damage are based on electrocardiographic changes, which appear within a few hours after the hemorrhage and disappear again after a few days. Obviously, such transient changes are of negligible importance in younger persons, but it is possible that cardiac disturbances may be of prognostic significance in older ones, and clinical experience would seem to indicate that such may occasionally be the case, particularly in the presence of already existing heart disease.

The problem of perforated ulcers is essentially surgical but should be competently faced by the internist, to whom the patient with this condition frequently first presents himself. The survey by Berson [139] is, therefore, of importance. It covers the experiences of an eighteen year period, including 154 consecutive patients with acute ulcer perforations. A relative infrequency was noted during the warm months, and the incidence of perforation in men was thirteen times that encountered in women. More than four fifths of the entire group had experienced ulcer

136. Black, D. A. K.: Blood Amino Acids in Hematemesis, Lancet **2**:309, 1941.

137. Bick, M., and Wood, I. J.: Some Observations on the Biochemical Changes Associated with Hemorrhage from the Stomach and Duodenum, M. J. Australia **28**:104, 1941.

138. Scherf, D.; Reinstein, H., and Klotz, S. D.: Electrocardiographic Changes Following Hematemesis in Peptic Ulcer, Rev. Gastroenterol. **8**:343, 1941.

139. Berson, H. L.: Acute Perforated Peptic Ulcers: An Eighteen Year Survey, Am. J. Surg. **56**:385, 1942.

symptoms prior to surgical intervention, and 3 had had recurrent perforations. Pneumoperitoneum was present in 80 per cent of the cases in which roentgenograms were taken. Perforation of duodenal ulcers was seven times as frequent as that of gastric ulcers, but the mortality was greater in patients with the latter lesions. Seventy per cent of the patients with cultures of peritoneal fluid positive for micro-organisms at the time of operation died. It is highly probable that recently introduced chemotherapeutic agents would have modified these results to an appreciable degree. The total mortality rate was 15 per cent. The importance of the time element in the ultimate result after perforation of an ulcer is illustrated by the report of Henry,[140] who examined the peritoneal fluid obtained from a group of perforated peptic ulcers, micro-organisms being found to be present in the peritoneal cavity shortly after perforation. Gastric acidity is low at the time of operation, and bacteria occur in the gastric contents. The peritoneal fluid has a hydrogen ion concentration and a chloride content approaching those of blood plasma, and there is little evidence that there is any diminution of the bacterial growth either by gastric contents or by peritoneal fluid. Seley and Colp[141] report pathogenic micro-organisms in 30 per cent of benign ulcers studied, but, as usual, one would expect a much higher incidence of bacterial growth occurring in malignant lesions, possibly due to lower gastric acidity.

The role of the surgeon in the ulcer problem is discussed by Wangensteen,[142] who believes that all failures in the management of patients with ulcer treated either by medical or by surgical measures rise from inability to control gastric acidity. Whether such a concept is valid certainly remains an unsettled question at the present time, but his conclusions are undoubtedly correct—that subtotal gastrectomy at present is the most effective surgical procedure in controlling postoperative gastric acidity and is associated with the lowest incidence of postoperative recurrences. He believes that this operation may be done for ulcer and its complications, exclusive of perforation, with an operative risk of 2 per cent, provided adequate preoperative and postoperative measures are taken. A follow-up study by Walters and Cleveland[143] supports the contention that partial gastrectomy offers the best chance

140. Henry, C. M.: Peritoneal Fluid in Perforated Peptic Ulcers, Ann. Surg. **114**:155, 1941.

141. Seley, G., and Colp, R.: The Bacteriology of Peptic Ulcers and Gastric Malignancies: Possible Bearing on Complications Following Gastric Surgery, Surgery **10**:369, 1941.

142. Wangensteen, O. H.: The Surgeon and the Ulcer Problem, Illinois M. J. **80**:100, 1941.

143. Walters, W., and Cleveland, W. H.: Results of Partial Gastrectomy for Bleeding Duodenal, Gastric and Gastrojejunal Ulcer, Ann. Surg. **114**:481, 1941.

of a cure or of an amelioration of symptoms of bleeding peptic ulcer and the best prophylaxis against further hemorrhage. Eighty-seven per cent of 112 patients treated by partial gastrectomy for bleeding peptic ulcer obtained satisfactory results. These authors stress the necessity of removing the pyloric antrum in the course of all gastric resections, in order to obtain the most satisfactory results. Such a view is commonly held by most experienced gastric surgeons, who have tended to become more and more radical in their procedures in recent years. The time that has elapsed since the inauguration of this most radical form of subtotal resection is still too short, in my opinion, to settle this point adequately. An article by Connell,[144] for example, is of interest. He discusses the physiology of the stomach in relation to hydrochloric acid production, with particular reference to Edkin's theory that an antral hormone, gastrin, stimulates the secretion of fundic acid. He states correctly that this theory has not yet been proved either experimentally or clinically, and such doubt is implied in an article previously referred to by Ivy.[31] Connell suggests that subtotal resection be modified by preservation of the alkaline secreting antrum and the pyloric neuromuscular sphincter mechanism. Whether this suggestion is wise may be open to question, but the final conclusion in the light of previous experience in ulcer therapy is undoubtedly correct, namely, that because of various known factors, it is wise to refrain from drawing conclusions relative to results of therapeutic measures until after the lapse of at least five years. To date, follow-up studies of this length are still lacking. There can be no doubt that subtotal resection has reduced remarkably the incidence of recurrent ulcer, and it is true that many patients lead relatively normal comfortable lives after such an operation. It is also true, however, that an important number of persons who have been subjected to such radical surgical procedures recover strength and weight slowly after the operation and for a long time have a multiplicity of minor complaints which should not be overlooked. Subtotal resection is not a physiologic procedure, and it is still wise to question the rationale of such a maneuver in the hope that better surgical measures may be evolved in those cases in which the condition is intractable to medical treatment. Schwartz, Reingold and Necheles,[145] recognizing these facts, have made an investigation of the relation between blood sugar and general complaints following subtotal gastric resection. Their studies were undertaken because of observations on the complaints of dizziness, warmth, perspiration, palpitation and nausea, which are not infrequently residual

144. Connell, F. G.: Peptic Ulcer, Hydrochloric Acid and Edkins' Theory, Am. J. Surg. **53**:255, 1941.

145. Schwartz, A.; Reingold, I., and Necheles, H.: Investigation of the Relationship Between Blood Sugar and General Complaints Following Subtotal Gastric Resection, Am. J. Digest. Dis. **9**:151, 1942.

symptoms in patients subjected to subtotal gastrectomy. The studies indicated that they are not due to transient hypoglycemia, but the authors are inclined to attribute them to a distention of the upper portion of the small intestine following the ingestion of food. In many instances they could be prevented by the taking of frequent, small meals or relieved by lying down after the intake of food.

Gastric Cancer.—Attempts to produce experimental gastric cancer in animals continue to be made, and a report by Stewart and Lorenz [146] records the production of cancer in mice following local injection of 20-methylcholanthrene. The injections were made into the glandular mucosa of the pyloric portion of the stomach, which is not completely refractory to cancer induction. Unlike the results obtained in the production of tumors in the forestomach and the small bowel, the oral administration of this substance was not accompanied by carcinomatous changes in the pyloric portion of the stomach. Groups of rats and mice studied by Beck and Peacock [147] were fed a variety of repeatedly heated fats in addition to an adequate basal diet. Subsequent avitaminosis A appeared among the animals, and ulceration and papillomatosis of the forestomach were observed among those that died. Control animals did not show any gross pathologic lesions. Whether various factors, such as dietary deficiencies, gastric achlorhydria and the like, lead to the development of papillomatous or malignant changes in human beings is still a completely open question, but the results of experiments, such as the preceding ones, together with numerous clinical observations, would lead one to hope that evidence may eventually be obtained regarding the causative factors.

It is well to review from time to time the results of surgical treatment of malignant disease of the stomach. The results reported by Walters and his colleagues [148] are typical of the relatively successful surgical treatment of malignant growths of the stomach that has been reported in recent years. Examination of the results will show that the mortality rate has been progressively decreasing. In a large group of patients who did not have extensive carcinoma or metastases and who underwent gastric resection, these authors report a five year survival rate of nearly 30 per cent, a ten year survival rate of 20 per cent and a fifteen year survival rate of 15 per cent. An important diagnostic point is found in the statement that approximately one third of the

146. Stewart, H. L., and Lorenz, E.: Induction of Adenocarcinoma of the Pyloric Stomach in Mice by Methylcholanthrene, J. Nat. Cancer Inst. **2**:193, 1941.

147. Beck, S., and Peacock, P. R.: Gastro-Papillomatosis Due to Vitamin A Deficiency Induced by Heated Fats, Brit. M. J. **2**:81, 1941.

148. Malignant Lesions of the Stomach, editorial, J. A. M. A. **117**:1893 (Nov. 29) 1941.

patients who had carcinomatous lesions of the stomach which were resectable had symptoms of the so-called "ulcer type" and in the majority of these patients routine ulcer therapy resulted in a temporarily effective control of symptoms. Too much emphasis cannot be placed on the latter fact, inasmuch as a favorable result of medical treatment in relatively early cancer too frequently has led to a postponement of adequate diagnostic measures and therapy. The authors urge a more general acceptance of the fact that medical treatment of an ulcer type of dyspepsia should not be instituted without roentgen examination to determine the exact location and nature of the lesion. In a subsequent paper Walters [149] points out the success of subtotal resections in the treatment of benign gastric ulcer, the results being superior to those of similar operations for duodenal ulcer. At the time of publication Walters stated that he had not seen a case of recurrent benign ulceration in which half or more of the stomach was removed with the benign gastric lesion. Eusterman [150] emphasizes the fact that small ulcerating forms of gastric carcinoma not only may be clinically indistinguishable at times from benign lesions but may respond to medical treatment in such a favorable manner as to give an entirely wrong impression of their true nature. Failure to carry out adequate diagnostic procedures under such circumstances cannot be too strongly condemned. Eusterman points out the various diagnostic criteria that eventually lead to a decision as to the form of therapy indicated. It is rather unfortunate that in none of these articles is sufficient prominence given to the diagnostic possibilities of adequate examination by an experienced gastroscopist. Before resorting to radical surgical treatment of gastric ulceration, a combined examination by roentgen and gastroscopic methods undoubtedly offers the best possible control of the situation and in many instances provides perfectly adequate information as to complete healing and as to the benign nature of the lesion, something that frequently cannot be accomplished by roentgen studies alone. Eusterman adds 3 other cases to 2 previously reported of carcinoma *in situ*, a relatively rare condition. A rather discouraging report on the subject is that of Boyce.[151] Over a period of years only 2 of every 30 patients treated for cancer of the stomach in the New Orleans Charity Hospital could be submitted to gastrectomy, and the immediate mortality for this operation was over 50 per cent, the 200 latest surgical patients

149. Walters, W.: Gastric Ulcer, Carcinomatous Ulcer or Ulcerating Carcinoma? Ann. Surg. **115**:521, 1942.

150. Eusterman, G. B.: Carcinomatous Gastric Ulcer: Misleading Results of Medical Therapy, J. A. M. A. **118**:1 (Jan. 3) 1942.

151. Boyce, F. F.: Carcinoma of the Stomach in a Large General Hospital: A Comparative Study of Two Series of Surgical Cases from Charity Hospital of Louisiana at New Orleans, J. A. M. A. **117**:1670 (Nov. 15) 1941.

in this series presenting little improvement in end results over a similar series reported in 1933. The author rightly attributes failure to make early diagnoses for this particular group of patients, most of whom were taken from the lower economic levels, to lack of insistence on the part of physicians on adequate study of gastric complaints. Hinton,[152] in a discussion of the same subject, outlines the difficulties of diagnosis and treatment and also shows the relative rarity with which carcinoma develops in benign ulcer. As an indication of the trend of cancer studies at the present time, he cites the work done by many investigators attempting to find a connection between estrogens, androgens and the gastric mucosa as a possible factor in causation of carcinoma.

As a means of determining the prognosis in gastric carcinoma, the classification based on gastroscopic examination suggested by Baumann is discussed by Schindler and his associates.[153] Inasmuch as careful gastroscopy permits at least a relatively satisfactory use of this classification, it is of interest until further observations and studies have been made. According to this grouping, lesions classified as polypoid or noninfiltrating, carcinomatous ulcers have a relatively good prognosis; those classified as infiltrating, carcinomatous ulcers and diffuse infiltrating growths are associated with unfavorable end results after surgical intervention. That erroneous conclusions may be drawn at operation on the possible spread of gastric cancer to regional lymph nodes is indicated in a careful pathologic study by Coller, Kay and MacIntyre.[154] In 53 cases the lymph nodes were dissected from each operative specimen and examined individually after a rather exhaustive study. Evidence of metastases was found in three fourths of the cases in this study, in one fourth of the cases the growth had involved the duodenum and in one fourth of the cases the upper margin of the neoplasm could not be determined by palpation alone at the time of operation. There was no relation between the size of the neoplasm and the presence of lymphatic metastases. Small neoplasms were often associated with extensive nodal metastases. Fewer metastases were noted from polypoid neoplasms than from those of the sessile type. In a majority of the cases in which the regional nodes were not palpable or if palpable were not thought to be suggestive of a malignant growth, the cancer was subsequently shown to have metastasized. The authors insist on the necessity of including a wide zone of resection, whether palpable lymph nodes are present or not, in order to increase the likelihood of cure.

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152. Hinton, J. W.: Carcinoma of Stomach, Bull. New York Acad. Med. **17**:829, 1941.

153. Schindler, R.; Steiner, P. E.; Smith, W. M., and Dailey, M. E.: The Classification of Gastric Carcinoma, Surg., Gynec. & Obst. **73**:30, 1941.

154. Coller, F. A.; Kay, E. B., and MacIntyre, R. S.: Regional Lymphatic Metastases of Carcinoma of the Stomach, Arch. Surg. **43**:748 (Nov.) 1941.

Justification for the most radical form of surgical treatment, even if it involves total gastrectomy, is to be found in the more recent reports of an increasing number of survivals following operation based on improved surgical technic. Even with complete removal of the stomach, as pointed out by Jones,[155] Donald [156] and Morton,[157] it is possible to hope for a progressively increased survival rate and relative freedom from incapacitating symptoms with adequate postoperative care.

Duodenum (Sphincter of Oddi).—The behavior of the sphincter of the common bile duct and its relation to the processes of normal digestion in the intestinal tract have been the subjects of study by Necheles and Kozoll.[158] The resistance of the sphincter and its response to a number of substances were tested on 10 human subjects after operation and drainage of the common bile duct. Parallel experiments were carried out on dogs in which the activity of the gallbladder and the duodenum and sphincter resistance were measured simultaneously. Drugs of the epinephrine group had variable effects on sphincter tone in human subjects and on the mechanism of evacuation of the gallbladder in dogs. Symptoms produced by the administration of atropine were followed by increased sphincter resistance in the patients studied. The effects of papaverine were inconstant. Codeine phosphate also increased sphincter resistance greatly both in the human subjects and in the experimental animals. Prostigmine usually increased sphincter tone considerably. Magnesium sulfate was followed by vigorous contractions both of the sphincter and of the duodenum in the dog but by only a slight increase in sphincter tone in human beings. The hydrochloride of diphenylacetyldiethylaminoethanol, glyceryl trinitrate and amyl nitrite depressed the tone of the sphincter, particularly when it was high after the administration of other drugs like codeine. In the patients studied postoperatively, it was noted that coughing, the occurrence of nausea and passage of stools increased sphincter resistance, as did ingestion of a meal. The sphincter seemed to be subject to psychologic effects, inasmuch as the sight or odor of meals produced considerable tonus waves. These results are probably to be accepted as an accurate interpretation of physiologic responses occurring in normal human beings, but it should be remembered that in half of the experiments made on

155. Jones, T. E.: Total Gastrectomy: Report of a Case, Cleveland Clin. Quart. **8**:225, 1941.

156. Donald, C. J., Jr.: Total Gastrectomy: Report of a Case, Proc. Staff Meet., Mayo Clin. **16**:446, 1941.

157. Morton, C. B., II: Total Gastrectomy: Indications for Operation with a Report of Four Cases, Arch. Surg. **44**:72 (Jan.) 1942.

158. Necheles, H., and Kozoll, D. D.: A Study of the Sphincter of Oddi in the Human and in the Dog, Am. J. Digest. Dis. **9**:36, 1942.

patients in this particular study surgical treatment of the gallbladder had already preceded observation and may have modified the responses to some extent.

The effect of bile flow through the sphincter, probably as a result of relaxation of the sphincter, was observed by Bergh [159] in human subjects, with results confirming the suggestions of previous investigators. A fatty meal, consisting of egg yolks and cream, apparently produced relaxation of the sphincter, but fresh olive oil had little effect. After a protein meal relaxation occurred only once, and no significant effect was observed after ingestion of carbohydrates.

Focal disease limited to the sphincter of the common bile duct is rare. For this reason the report of Sharpe and Comfort [160] on 40 cases of carcinoma of the papilla of Vater is worthy of study. In only 1 of these cases was the possibility of carcinoma of the ampulla suggested before operation, although in 38 the diagnosis indicated that the clinician knew that obstruction of the common bile duct was present. Obviously, jaundice was a constant feature, but in many instances it was protracted and was fluctuating in its intensity. The authors point out that there is no typical clinical picture or no typical physical findings. Pain is a constant feature, and it is of extreme interest that chills and fever were present in over half of the cases, as was diarrhea. The obvious conclusion from such a study is that in the absence of clinical improvement or adequate diagnostic observations surgical intervention is indicated.

Diverticula and Unusual Tumors.—It is usually admitted that diverticulosis of various portions of the digestive tract may represent an adventitious condition and may not cause any symptoms. This is particularly true of diverticula of the stomach and the upper portion of the small intestine. Gastric diverticula are rare, and as a rule, they are encountered near the cardiac orifice, as is pointed out by Reineke,[161] who reports 4 cases of gastric diverticulum so situated. The diagnosis is dependent on roentgen examination, and treatment when necessary may involve simple medical measures, including postural drainage or, occasionally, resection. Two other instances of this uncommon condition are reported by Schmidt and Walters,[162] who review the classification and symptomatology in detail. They believe that gastroscopy is

159. Bergh, G. S.: The Effect of Food Upon the Sphincter of Oddi in Human Subjects, Am. J. Digest. Dis. **9**:40, 1942.

160. Sharpe, W. S., and Comfort, M. W.: Carcinoma of the Papilla of Vater: Clinical Features in Forty Cases, Am. J. M. Sc. **202**:238, 1941.

161. Reineke, H. G.: Diverticula of the Upper End of the Stomach, Am. J. Roentgenol. **46**:650, 1941.

162. Schmidt, H. W., and Walters, W.: Diverticula of the Stomach, Am. J. Surg. **52**:315, 1941.

of aid in differentiating the types of diverticula and in demonstrating the presence or absence of pancreatic tissue or benign growths in those instances in which the diverticula are essentially of the traction type. Kozinn and Jennings [163] add a case to the small number of previously reported instances of jejunal diverticula. Like other diverticula they are usually thought to be either congenital or acquired. The authors correctly point out the lack of symptoms attributable to most of these abnormalities, but, as in the case they report, they may cause either acute abdominal conditions due to perforation and peritonitis or bleeding, the latter being more common in children.

Meckel's diverticulum is a relatively common condition and frequently results in bleeding in children or in obstructive symptoms. Two instances of such an occurrence are reported by Conrad.[164] A different type of complication is mentioned by Maddock and Coventry [165] in a case report of perforation of an ulcer of the ileum occurring opposite a Meckel diverticulum in a young child, another rather characteristic complication of this condition. As is frequently true, in this case and in 2 reported by Waugh and his colleagues [166] heterotopic gastric mucosa was present in the diverticulum, with resulting peptic ulceration of the ileum opposite the stoma. An unusual complication is that reported by Lium and Ladd [167] in an elderly man in whom acute Meckel's diverticulitis complicated a strangulated left inguinal hernia. Occasionally, Meckel diverticula are complicated by the local appearance of new growths. Albright and Sprague [168] add another to 6 previously reported cases of primary adenocarcinoma arising in such a diverticulum. Koucky and Beck [169] report a still more rare condition, a perforated leiomyoma of a Meckel diverticulum.

Unusual forms of growth, benign or otherwise, occur with sufficient frequency at various levels in the gastrointestinal tract to warrant only passing comment. Because of the variety of conditions involved, how-

163. Kozinn, P. J., and Jennings, K. G.: Jejunal Diverticulitis: Its Occurrence in a Two-Year-Old Girl, Am. J. Dis. Child. **62**:620 (Sept.) 1941.

164. Conrad, N. A.: Meckel's Diverticulum: Report of Two Cases, Am. J. Surg. **52**:267, 1941.

165. Maddock, W. G., and Coventry, M. B.: A Perforated Ulcer of the Ileum Opposite a Meckel's Diverticulum, Surg., Gynec. & Obst. **73**:105, 1941.

166. Waugh, J. M.; Herrell, W. E., and Crumpacker, L. K.: Peptic Ulcer in Meckel's Diverticulum Causing Intrinsic Intestinal Obstruction: Report of Two Cases, Surgery **11**:385, 1942.

167. Lium, R., and Ladd, S. T.: Left Inguinal Hernia with Acute Meckel's Diverticulitis and Peritonitis, New England J. Med. **226**:15, 1942.

168. Albright, H. L., and Sprague, J. S.: Primary Adenocarcinoma in a Meckel's Diverticulum, New England J. Med. **226**:142, 1942.

169. Koucky, J. D., and Beck, W. C.: Perforated Leiomyoma of Meckel's Diverticulum: Report of Case, Surgery **10**:636, 1941.

ever, it is worth while to enumerate some of them briefly, particularly because the diagnosis of tumor of the digestive tract is being made with a rapidly increasing frequency. Rumold [170] contributes examples of an extremely rare condition, submucous lipoma of the stomach, 32 cases having been recorded in the literature prior to his report. Lemon and Broders [171] give a fairly comprehensive clinical and pathologic study of leiomyosarcoma, hemangioendothelioma, or angiosarcoma, and fibrosarcoma of the stomach. Fourteen cases of histologically proved gastric sarcoma are included in the report. Surgical removal of these tumors is, of course, indicated, and the prognosis, while guarded, is better than that of lymphosarcoma or carcinoma. A leiomyoma of the stomach was successfully removed by Halperin,[172] and reports of 2 successful operations on gastric hemangiomas are added by Morton and Burger,[173] in 1 case the growth being found on gastroscopy. A report by Koenig and Culver [174] of 2 cases of Hodgkin's disease involving the stomach confines itself largely to a description of the roentgen findings, which unfortunately are not sufficiently characteristic to differentiate this condition from other infiltrating ulcerative lesions. Another rare occurrence is acute perforation of lymphosarcomatous ulcer of the stomach, mentioned by Koucky and his associates.[175] Symptoms in a boy of 14 years were of only one week's duration before the acute perforation took place. The nature of the ulcerative process was determined at operation by biopsy, and satisfactory recovery occurred. In spite of the repeated statement that perforation is a common complication of gastric lymphosarcoma, so far the authors have found only 4 other instances of a similar occurrence. One of the rarest forms of gastric tumor is recorded by Fuller,[176] who describes a case of neurilemmoma of the wall of the stomach complicated by ulceration of the underlying mucosa. The clinical picture in this instance was that of peptic ulcer. The report is of further interest in that it brings out a point that is occasionally forgotten—namely, that new growths, either primary or benign, may

170. Rumold, M. J.: Submucous Lipomas of the Stomach, Surgery **10**:242, 1941.

171. Lemon, R. G., and Broders, A. C.: A Clinical and Pathological Study of Leiomyosarcoma, Hemangioendothelioma or Angiosarcoma, and Fibrosarcoma of the Stomach, Surg., Gynec. & Obst. **74**:671, 1942.

172. Halperin, P. H.: Leiomyoma of the Stomach, Missouri M. J. **38**:235, 1941.

173. Morton, C. B., and Burger, R. E.: Hemangioma of the Stomach: Review of the Literature and Report of Two Cases, Surgery **10**:891, 1941.

174. Koenig, E. C., and Culver, G. J.: Hodgkin's Disease Involving the Stomach: Report of Two Cases, Am. J. Roentgenol. **46**:827, 1941.

175. Koucky, J. D.; Beck, W. C., and Atlas, J.: Acute Perforation of Lymphosarcomatous Ulcer of the Stomach, Ann. Surg. **114**:1112, 1941.

176. Fuller, R. H.: Neurilemmoma of the Stomach with Peptic Ulcer, Arch. Path. **32**:441 (Sept.) 1941.

cause superficial ulceration of the gastric mucosa, with a resulting clinical picture entirely similar to that of peptic ulcer. Unless careful diagnostic procedures are carried out, the underlying cause of the disease is frequently overlooked because of the favorable response to medical therapy. In this case the tumor and the ulcer were resected, with subsequent recovery. Another curious occurrence is noted by Cohn and associates,[177] who encountered gastric disease in a patient who had been ingesting a preparation containing kaolin for a long time. Clinical and roentgen examination failed to reveal any gastric abnormality, but gastroscopy indicated a prepyloric tumor, which, however, was not seen in the gross resected stomach. Microscopic studies proved the lesion to be a granuloma, with the type of foreign body giant cell present in the lesions of silicosis. Mineralogic studies confirmed the presence of silica in the gastric tissues. The authors were able to reproduce in rabbits similar lesions secondary to silica irritation.

The relative rarity of tumors of the small intestine is indicated in a statistical study of such lesions by Morison,[178] who reviews the results of 2,434 autopsies and 10,705 biopsies. In this large number of specimens examined 21 primary tumors of the small bowel were encountered among which were 5 lipomas, 3 adenomas, 2 leiomyomas, 1 pedunculated subserous fibroma, 2 argentaffinomas, 4 adenosarcinomas and 4 lymphosarcomas. In addition, there were 4 examples of pancreatic heterotopia. There is nothing new in the article, but it illustrates more or less clearly the incidence and occurrence of various forms of unusual tumor in the small bowel, a preoperative diagnosis of the nature of which is rarely possible. Obstructive symptoms ranging from mild peristaltic unrest to acute intussusception are frequently encountered, however, and hemorrhage is not uncommon. A similar report is that by Morrison and Donath,[179] who record 45 tumors of the small bowel that were encountered in the examination of over 25,000 autopsy reports and a large number of reports of surgical procedures and biopsies. There were 26 malignant and 19 benign tumors; they were of varying types, as was the case in Morison's report. The incidence of submucous lipoma of the small intestine is apparently greater than that noted in the stomach, and Botsford and Newton[180] report a case of intussusception due to this condition and review 95 other cases of a similar condition.

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177. Cohn, A. L.; White, A. S., and Weyrauch, H. B.: Kaolin Granuloma of the Stomach, J. A. M. A. **117**:2225 (Dec. 27) 1941

178. Morison, J. E.: Tumors of the Small Intestine, Brit. J. Surg. **29**:139, 1941.

179. Morrison, W. A., and Donath, D.: Tumors of the Small Intestine, California & West. Med. **55**:235, 1941.

180. Botsford, T. W., and Newton, F. C.: Intussusception in an Adult Due to Submucous Lipoma of the Ileum, Surgery **10**:265, 1941.

Golden and Stout [181] present a careful discussion of one rare type of tumor of the gastrointestinal tract—namely, that originating in the smooth muscle of the tract itself or in the retroperitoneal tissue. Sixty cases of it are described, in 30 of which the tumor was accidentally encountered at operation or at autopsy. The paper concerns itself chiefly with 30 cases in which presenting symptoms were due to the tumor. The distribution in this series was as follows: stomach, 8; duodenum, 2; jejunum, 1; ileum, 3; a Meckel diverticulum, 1; colon, 2; rectum, 5, and retroperitoneal space, 8; two thirds of the tumors were malignant. In discussing the prognosis following adequate surgical treatment the authors make the important point that the outlook depends as much on the anatomic site of the tumor as on its histologic character. Tumors of the stomach, jejunum, ileum and colon are restrained for a long time by the barrier of the peritoneum, so that they can be entirely removed, usually with success. The anatomic peculiarities of the duodenum, rectum and retroperitoneum render difficult or impossible complete removal. Warren and Lulenski [182] present the results of a study of 28 cases of primary solitary lymphoid tumors encountered in a series of 3,132 malignant lesions of the digestive tract. Half of these occurred in the stomach. In this series the prognosis of this solitary form was little better than that of generalized lymphoid tumors, but in their discussion the authors point out that in many cases long survival periods and possibly complete cures have been obtained by adequate surgical treatment and radium therapy.

Only 3 proved cases of primary cancer of the duodenum were encountered among 16,000 admissions to a hospital for patients with cancer, according to Ritvo and Hewes.[183] The symptoms and the roentgen evidence associated with this almost entirely hopeless condition are described by the authors. An odd case of Hodgkin's disease involving the duodenum is reported by Pusch.[184] Successful removal of primary adenocarcinoma of the jejunum is reported by Cornell and Hauser [185] and by Craig,[186] and a general discussion of this particular condition is included in the reports. Sarcoma of the small bowel is

181. Golden, T., and Stout, A. P.: Smooth Muscle Tumors of the Gastrointestinal Tract and Retroperitoneal Tissues, Surg., Gynec. & Obst. **73**:784, 1941.

182. Warren, S., and Lulenski, C. R.: Primary, Solitary Lymphoid Tumors of the Gastro-Intestinal Tract, Ann. Surg. **115**:1, 1942.

183. Ritvo, M., and Hewes, F. L.: Clinical and Roentgen Manifestations of Carcinoma of the Duodenum, Radiology **38**:7, 1942.

184. Pusch, L. C.: Hodgkin's Disease of the Duodenum, Pennsylvania M. J. **45**:20, 1941.

185. Cornell, N. W., and Hauser, L. A.: Primary Adenocarcinoma of the Jejunum, Am. J. Surg. **53**:177, 1941.

186. Craig, W. J.: Primary Carcinoma of the Jejunum: A Case Report, Brit. J. Radiol. **14**:162, 1941.

thoroughly discussed by Frank, Miller and Bell,[187] who add 4 cases to the 114 previously reported. An illustration of the difficulty underlying the diagnosis of tumor of the small bowel is presented by Shulman.[188] This author reports a case of primary lymphosarcoma of the jejunum in which approximately 4 feet (122 cm.) of the intestine was involved, without producing anything but mild symptoms. The discovery of the growth was based on a routine roentgen examination for a suspected peptic ulcer.

A complete discussion of the various aspects of carcinoids of the appendix is found in a report by Wengen.[189] He reviews his own 14 cases observed in the Basel Clinic, Basel, Switzerland, and comments on the variety of terms that have been used to designate these essentially benign tumors, which in most instances are completely cured by appendectomy. Gault and Kaplan[190] add another case to 129 previously reported instances of submucous lipomas of the colon. These tumors have the characteristic complication of intussusception in a fairly high percentage of cases, and the authors comment correctly on the fact that in cases of suspected pathologic conditions in the colon in which there is a long history of recurring attacks of pain, constipation and bloody diarrhea, unassociated with loss of weight or with cachexia, the presence of a benign lesion should be suspected. Hemangioma of the large bowel has been reported in only 20 instances, according to Hunt,[191] who included 2 of his own cases in this number, 1 involving the cecum and appendix and encountered in the course of routine cholecystography for gallstones and the other occupying the rectosigmoid portion of the colon and the entire rectum. The predominant symptom obviously is hemorrhage, and the author points out that unlike hemangioma of the small bowel, intussusception has not been reported in association with colonic lesions.

An additional cause of hematemesis and melena is included in this section, namely, hereditary hemorrhagic telangiectasis. Griggs and Baker[192] report 3 cases of this unusual familial condition. The bleeding, as usual, was believed to be due to telangiectatic areas in the stomach or elsewhere in the intestinal tract.

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187. Frank, L. W.; Miller, A. J., and Bell, J. C.: Sarcoma of the Small Intestine, Ann. Surg. **115**:544, 1942.

188. Shulman, S.: Primary Lymphosarcoma of the Jejunum, Am. J. Roentgenol. **46**:182, 1941.

189. Wengen, H. C.: Aspects of Carcinoids of Appendix, Klin. Wchnschr. **20**: 316, 1941.

190. Gault, J. T., and Kaplan, P.: Submucous Lipoma of the Colon: Report of Case, Am. J. Surg. **53**:145, 1941.

191. Hunt, V. C.: Hemangioma of the Large Bowel, Surgery **10**:651, 1941.

192. Griggs, D. E., and Baker, M. Q.: Hereditary Hemorrhagic Telangiectasia with Gastro-Intestinal Bleeding, Am. J. Digest. Dis. **8**:344, 1941.

Intestinal Obstruction.—The problem of intestinal obstruction has received considerable attention, both from the point of view of experimental investigation and from that of clinical observation. Antoncic and Lawson [193] carried out balloon studies of motility in obstructed loops of small bowel in unanesthetized dogs. Comparisons were made in some of the animals with the motility in unobstructed distal segments. The range of pressure in closed loops was found to be considerably above the range in the distal, unobstructed intestine. Contractility was usually considerably greater in the obstructed loops, and neither pressure nor contractility was found to diminish toward the end of the survival period unless perforation occurred. There was no loss in irritability to intravenous administration of epinephrine, even in the terminal stages of obstruction. These results are in agreement with those of previous investigators, and the data suggest that terminal ileus is a concomitant of peritonitis, rather than of obstruction. The authors were unable to obtain evidence supporting Alvarez' hypothesis that reversal of the rhythmic gradient is responsible for stasis and vomiting in cases of intestinal obstruction.

The mechanism of deflation hyperemia in the intestine was carefully studied by Lawson,[194] who found that the increased arterial flow into loops of small intestine following periods of low pressure distention (deflation hyperemia) is associated with an augmented venous flow and usually is considerably greater in volume than the demonstrable reduction in volume of the intestinal walls during the distention. He considers that the greater part of the deflation hyperemia is due to a persistence of a resistance-lowering mechanism set up by stretch of the intestinal walls. Gatch and Battersby [195] also studied the effect of bowel injury by distention with particular relation to its effect on the volume and concentration of the blood. Distention great enough to injure the bowel is described as passing through two stages noted in human beings and in experimental animals. In the first stage the bowel is tense and anemic; in the second stage it is flaccid and congested. It passes from the first to the second stage when the wall stretches enough to permit resumption of the flow of the blood in fair volume through its capillaries. Injury occurs in the first stage; recovery, in the second. Most of the albuminous fluid encountered in the peritoneal cavity in the presence of obstruction of the bowel accumulates in the first stage of distention and varies with the duration of this first stage and with the degree of

193. Antoncic, R. F., and Lawson, H.: The Muscular Activity of the Small Intestine, in the Dog, During Acute Obstruction, Ann. Surg. **114**:415, 1941.

194. Lawson, H.: The Mechanism of Deflation Hyperemia in the Intestine, Am. J. Physiol. **134**:147, 1941.

195. Gatch, W. D., and Battersby, J. S.: The Two Stages of Bowel Distention: Study of Bowel Injury by Distention and Its Effect on the Volume and Concentration of the Blood, Arch. Surg. **44**:108 (July) 1942.

obstruction to the flow of blood in the wall of the distended bowel. The protein content of peritoneal fluid is about half that of plasma, and it is suggested that damage to the capillaries by intestinal distention is evidently not so serious as that due to burns or to inflammation, which makes the capillary endothelium incapable of holding back the large globulin molecules. The cyanosis of the bowel in the second stage of distention is due to vasomotor paralysis and to the relaxation of the tissues which support the capillaries. The authors believe that it is not due to venous obstruction.

Lawson and Ambrose [196] also studied the utilization of blood oxygen by the distended intestine and showed that during moderate distention of the ileum and the jejunum in dogs, there is usually a marked rise in the oxygen content of the venous blood returning from the loop, with a striking reduction in the arteriovenous oxygen difference. The authors offer their data as incomplete evidence for the opening of low resistance vascular shunts in the distended intestine, which short circuit some of the tissues of the intestinal wall, depriving them of their oxygen supply, and which at the same time provide for the maintenance of an undiminished total volume flow of blood. Gatch and Battersby [197] also report the results of studies on the effect of asphyxia caused by distention of the bowel on the concentration of the blood. Prolonged distention of the stomach and the small bowel, with pressures too low to damage these organs, was found to result in the death of the experimental animals. These investigators believe that asphyxia due to interference with respiration was the cause of death and state that all of the effects of distention can be produced by prolonged limitation of air supply. Blood concentration, which was observed in these experiments, did not seem to be the primary cause of death and could be prevented by the administration of adequate quantities of plasma. Distention of the stomach was more rapidly fatal than distention of the small bowel, whereas distention of the large bowel was comparatively harmless. The lethal effects of such maneuvers seemed to depend on the degree of interference with respiration caused by local areas of distention.

Schnedorf and Orr [198] studied the effect of distention of the small intestine on the flow of bile and of urine in dogs. As has already been

196. Lawson, H., and Ambrose, A. M.: The Utilization of Blood Oxygen by the Distended Intestine, Am. J. Physiol. **135**:650, 1942.

197. Gatch, W. D., and Battersby, J. S.: Effect of Asphyxia Caused by Bowel Distention on the Concentration of the Blood, Arch. Surg. **44**:319 (Feb.) 1942.

198. Schnedorf, J. G., and Orr, T. G.: The Effect of Small Intestinal Distention upon Bile and Urine Flow: Its Possible Relationship to the Hepatorenal Syndrome, Am. J. Digest. Dis. **8**:303, 1941; The Effect of Distention of the Small Intestine, Anoxemia and Oxygen Therapy upon the Flow of Bile and Urine in the Dog: Relationship to the Hepatorenal Syndrome, Surg., Gynec. & Obst. **74**:446, 1942.

noted in distention of the large bowel, hepatic function was seen to be impaired, as evidenced by reduction in the flow of bile. In these experiments a somewhat similar reduction of renal function was also observed, apparently as a later phenomenon. Reductions in bile flow of as great as 40 per cent below the control level were obtained as a result of increased intraenteric pressures, and a further decrease was noted when intestinal distention was produced sufficient to cause a real decrease in the flow of portal blood. Oxygen therapy lessened this inhibition in bile flow in all of the dogs treated. The authors feel that inhibitory nervous reflex, decreased blood flow and anoxemia probably are factors involved in decreasing hepatic function in conditions of intestinal obstruction. Inhalations of high concentrations of oxygen are thought to be indicated when anorexia, with a resulting tendency to acholia and anuria, is observed in cases of intestinal obstruction. Whether or not such a mechanism is operative in the so-called "hepatorenal syndrome," as suggested by Shnedorf and Orr, is highly speculative.

The phenomenon of so-called "leukocyte exhaustion" in intestinal obstruction is discussed by Harris and Feldheym [199] and by Van Duyn.[200] The former authors report a series of 10 cases of obstruction of the small bowel in which daily postoperative white cell counts showed marked leukopenia in the immediate postoperative period of one to seven days. This leukopenia was not associated with surgical sepsis and did not necessarily indicate a fatal prognosis. Van Duyn contributes more detailed comments on the role of abdominal distention in leukocyte exhaustion and cites the results of white cell studies in 6 cases of leukocytic exhaustion with abdominal distention in the absence of severe infection. The so-called "pure degenerative" blood picture, that is, one associated with leukopenia not combined with severe infection, is characterized by low to leukopenic white cell counts, normal to neutropenic percentages of neutrophils, absence of myelocytes, normal to increased percentages of lymphocytes and monocytes and presence of eosinophils. Schilling has previously pointed out that such a differential count does not constitute an unfavorable clinical finding. Such a "degenerative" type of white cell failure may also be encountered in diseases of the gastrointestinal tract, other than those associated with obvious abdominal distention, such as typhoid, dysentery and colitis. On the other hand, Van Duyn believes that a shift to the so-called mixed "degenerative-regenerative" picture, in which regenerative elements or conditions are encountered, such as neutrophilia, myelocytes, monocytopenia and the absence of eosinophils, is usually of serious prognostic significance.

199. Harris, F. I., and Feldheym, J. S.: Leukocyte Exhaustion in Intestinal Obstruction, Am. J. Surg. **54**:417, 1941.

200. Van Duyn, J., II: Role of Abdominal Distention in Leukocyte Exhaustion, Arch. Surg. **44**:339 (Feb.) 1942.

Auscultation of the abdomen has been employed for many years in an attempt to obtain further information as to the presence or absence of an obstructive process or of peritonitis with paralytic ileus. Stevens [201] discusses this method of examination and attempts to prove that it may be a valuable adjunct to other diagnostic methods in cases of early intestinal obstruction and acute appendicitis. The author believes that as long as peristaltic sounds are heard, the bowel is not completely devitalized and, therefore, a good chance for recovery exists. In the case of intestinal obstruction, variations in the quality and the activity of peristaltic sounds are discussed in relation to morbid changes in the bowel. Whether such nice conclusions can be drawn in individual cases is open to some doubt, but there is little doubt that abdominal auscultation is used too infrequently both by surgeons and by internists in an attempt to clarify the status of any given cause of abdominal distention. The article is of importance merely to renew interest in an approved but not sufficiently utilized diagnostic method. An excellent and complete review of the clinical aspects of intestinal obstruction and strangulation is presented by Aird.[202] The article should be of interest primarily to the surgeon, but because of its completeness it should be read by the general physician as a help in evaluating the morbid influences underlying intestinal obstruction and strangulation. One possible aid in the diagnosis of strangulation of the bowel is considered by Hill and his collaborators.[203] As has occasionally been noted clinically, peritoneal aspiration in the presence of a strangulated bowel not infrequently yields a profuse exudate, which is cherry red or pink. Hill and his associates produced strangulated loops of bowel in dogs and within four hours were able to demonstrate the presence of a peritoneal exudate of this character. The exudate was extremely toxic when injected intravenously into another animal and always contained micro-organisms. Such a diagnostic procedure, although not usually necessary, should not be overlooked in an occasional case in which the diagnosis is difficult.

Various types of gastrointestinal obstruction, partial or complete in degree, with clinical comments are scattered throughout the literature. One unusual occurrence is that noted by O'Donnell and Klein,[204] who report a case of congenital pyloric stenosis occurring in both members

201. Stevens, N. C.: The Value of Auscultation of the Abdomen in Intestinal Obstruction, New England J. Med. **226**:87, 1942.

202. Aird, I.: Morbid Influences in Intestinal Obstruction and Strangulation, Ann. Surg. **114**:385, 1941.

203. Hill, F. C.; O'Loughlin, B. J., and Stoner, M.: Peritoneal Aspiration in the Diagnosis of Strangulated Bowel, Surg., Gynec. & Obst. **74**:121, 1942.

204. O'Donnell, F. T., and Klein, J. M.: Pyloric Stenosis in Nonidentical Twins, Am. J. Dis. Child. **62**:1025 (Nov.) 1941.

of a set of nonidentical twins. They also mention 2 brothers with this condition, who were operated on two years apart. A table of cases of similar conditions previously reported in the literature is appended. The authors infer that these cases afford additional evidence in support of the theory of the hereditary pathogenesis of some tumors. Congenital duodenal obstruction is an uncommon condition, which is highly fatal in the absence of prompt diagnosis and treatment. White and Collins [205] give the details of 4 cases in which they personally treated the patients and point out the important diagnostic and therapeutic considerations. The presence of bile in the vomitus, which is a persistent symptom, should lead to a suspicion of obstruction below the common bile duct, and the advisability of a careful but relatively simple roentgen examination is properly considered. Operative procedures, which afford the only proper therapeutic measure, should be accompanied by careful treatment of dehydration and shock, plasma transfusions being particularly indicated.

The whole question of intestinal obstruction from gallstones is again discussed by Foss and Summers,[206] who summarize the essential clinical features of such a condition. Of a collective series of 150 patients suffering from such a complication, 15 per cent did not present a history suggestive of disease of the gallbladder. The usual site of obstruction is in the terminal portion of the ileum, the gallstones having almost always passed through a spontaneous cholecystoduodenal fistula. A most unusual manifestation of this condition is mentioned by Cahill,[207] who reports a case of obstruction of the sigmoid flexure of the colon by a large biliary calculus.

Paralytic ileus is not usually associated as a complication accompanying trauma with resulting fractured ribs. Altemeier and Wadsworth [208] discuss 10 cases of such a condition occurring among 454 patients with fractured ribs in whom paralytic ileus was a serious complication. Only 5 cases have been previously reported. In 8 of the 10 cases of ileus following rib fracture the break occurred within 5 cm. of the lateral vertebral border, and the authors speculate on the probability of the intestinal obstruction being associated with an irritation of the thoracic sympathetic ganglions and the splanchnic nerves. Experimental stimulation of the splanchnic nerves produced relaxation and cessation of move-

205. White, C. S., and Collins, J. L.: Congenital Duodenal Obstruction, Arch. Surg. **43**:858 (Nov.) 1941.

206. Foss, H. L., and Summers, J. D.: Intestinal Obstruction from Gallstones, Ann. Surg. **115**:721, 1942.

207. Cahill, J. A.: Obstruction of the Sigmoid Flexure by a Large Stone, Am. J. Surg. **52**:285, 1941.

208. Altemeier, W. A., and Wadsworth, G. H.: Ileus Following Fractured Ribs, Ann. Surg. **115**:32, 1942.

ment of the small bowel. The authors suggest that if the presence of a ruptured intra-abdominal viscus can be ruled out, such a complication of trauma is best treated without operation.

Mattson and Larson [209] comment on a frequently unsuspected cause of intestinal obstruction, namely, food itself. They point out that many cases of so-called "ptomaine poisoning" and intestinal upsets due to food in reality may be short-lived intestinal obstruction due to a food bolus. As proof of such a hypothesis 2 cases of intestinal obstruction due to a large bolus of food, proved at operation, are recorded. Colp [210] discusses 5 cases of obstruction of the large intestine, in which a preoperative diagnosis of a malignant growth was made but in which subsequent developments warranted the diagnosis of muscular spasm as the cause of obstruction. Acceptance of such a mechanism as the cause of lasting intestinal obstruction may seem somewhat unwarranted unless adequate diagnostic procedures are carried out. It would seem that in most instances such a diagnosis would rarely be tenable, but the author's description of individual cases is reasonably convincing, and the article is highly provocative. When one considers the intense and lasting spasm caused by compounds containing lead or morphine and the sharply localized areas of intense spasm that can be easily palpated in patients suffering from acute attacks of "mucous colitis," it does not appear altogether improbable that an occasional case of colonic obstruction may occur from spasm alone.

A clinical diagnosis of acute cecal volvulus is seldom made, since there are no diagnostic criteria that are pathognomonic of this condition. Such a possibility must be considered in cases of intestinal obstruction of obscure origin, however, and for this reason the reports of Browne and McHardy [211] and of Wolfer and his associates [212] should be mentioned. The mechanism underlying such an occurrence is not difficult to visualize when one considers the large number of mobile cecums observed in routine roentgen examinations.

An unusual type of intussusception is that reported by Rossien,[213] who cites a case of chronic, spontaneous, reducing and relapsing

209. Mattson, H., and Larson, E. A.: Intestinal Obstruction Due to Food, Minnesota Med. **24**:559, 1941.

210. Colp, R.: Colonic Spasm as Cause of Intestinal Obstruction, Surgery **10**:270, 1941.

211. Browne, D. C., and McHardy, G.: Acute and Chronic Cecal Volvulus, Am. J. Digest. Dis. **9**:177, 1942.

212. Wolfer, J. A.; Beaton, L. E., and Anson, B. J.: Volvulus of the Cecum, Anatomical Factors in Its Etiology: Report of a Case, Surg., Gynec. & Obst. **74**:882, 1942.

213. Rossien, A. X.: Intussusception: Report of an Unusual Adult Case, Am. J. Roentgenol. **46**:832, 1941.

intussusception of the transverse colon into the hepatic flexure. The condition was observed by roentgen examination and correctly interpreted. A simple surgical maneuver of possible value is mentioned by Ireland,[214] who refers to injections of glycerin given to 2 patients with irreducible intussusceptions. In each instance the substance was injected between the intussuscipiens and the intussusception, with successful subsequent reduction.

There can be little doubt that intestinal suction has proved of inestimable therapeutic value in the treatment of an important number of cases of intestinal obstruction since the method was introduced by Wangensteen. The addition of the Miller-Abbott tube has rendered still further help in the treatment of selected cases of this disorder. There is still at times confusion as regards the proper indications for intestinal intubation and constant suction. An excellent résumé is presented by Abbott [215] and should be read by all practicing physicians. In this article the diagnostic and therapeutic indications for intubation are clearly given. An indication of the value of intestinal suction in the treatment of intestinal obstruction is provided in an article by Blodgett.[216] This author contrasts the mortality occurring in 206 cases of mechanical obstruction in which treatment was without intestinal suction with the results obtained in 151 cases of a similar condition treated by intubation. For the former group the mortality was 17.3 per cent, whereas in the cases in which treatment was by intubation a lowering of the death rate to 7.9 per cent was obtained. Similarly, the mortality in 56 cases of obstruction with associated peritonitis in which treatment was without intestinal suction was 73 per cent, whereas in an almost equal group of cases in which treatment was with the aid of intubation the mortality was only 25 per cent. It is unfortunate that neither of these writers points out the dangers attending too enthusiastic intubation and suction of intestinal contents in cases of obstruction. There can be little doubt that such a measure is of great value therapeutically, but there can also be no question that in many instances too prolonged and too enthusiastic withdrawal of intestinal fluids above an obstructed area may lead to serious, if not fatal, results because of depletion and the postponement of adequate surgical treatment. In addition to the loss of electrolytes accompanying too enthusiastic and prolonged intestinal suction, there is the danger of hypoprothrombinemia, with resultant risk of spontaneous hemorrhage.

214. Ireland, J.: Treatment of Intussusception, Arch. Surg. **43**:418 (Sept.) 1941.

215. Abbott, W. O.: Indications for the Use of the Miller-Abbott Tube, New England J. Med. **225**:641, 1941.

216. Blodgett, J. B.: An Evaluation of Intestinal Suction in Intestinal Obstruction, Surgery **11**:739, 1942.

Such a possibility is carefully considered by Abbott and Holden [217] in a discussion of hypoprothrombinemia in intestinal disorders.

Parasitic Diseases.—With the existence of global war there can be no doubt that civilian, as well as military, physicians will be confronted with many hitherto more or less neglected disease conditions. A closer association with foreign populations, particularly in the tropics, will automatically make possible the transfer of so-called "tropical diseases" to more temperate climates. The prevalence of amebiasis in this country is generally recognized, but its actual incidence is not fully appreciated by physicians practicing in the more northern sections of the country. For this reason an article by Faust [218] on the prevalence of amebiasis in the western hemisphere is extremely timely and should be perused with a great deal of care. In spite of the discrepancies among various surveys already made in different parts of the country, many of which are too fragmentary or too limited in scope to provide an adequate basis for conclusions, Faust believes that amebiasis exists in an appreciable portion of the population of the western hemisphere from central west Canada to the Strait of Magellan. He feels certain that it is much more intensely endemic in the American tropics than in the temperate zones but makes the rather astounding estimate that in areas like the United States the incidence may average as high as 20 per cent, a figure possibly double that previously accepted. Evidence that such an estimate is not overdrawn may be found, for example, in an article on amebiasis in the Yakima Valley, Wash., by Lewis and Low.[219] Examination of a large number of stools over a period of five years revealed that amebas could be demonstrated in 21.5 per cent of 586 specimens, and of these, Endamoeba histolytica accounted for more than half. The unusually large number of Orientals inhabiting the Yakima Valley is a contributing factor, and the authors make a pertinent observation when they mention that purification of water by the chlorination-sedimentation method is ineffective against contamination by amebic cysts.

It is generally accepted that subclinical infection in human beings caused by Trichinella spiralis is extremely common, and a recent report by Most and Helpern,[220] who used the most careful digestion, press and microscopic methods, revealed that 22 per cent of 100 persons dying by violence in New York city showed evidence of human trichinosis.

217. Abbott, W. E., and Holden, W. D.: Hypoprothrombinemia in Intestinal Disorders, Am. J. Surg. **53**:215, 1941.

218. Faust, E. C.: The Prevalence of Amebiasis in the Western Hemisphere, Am. J. Trop. Med. **22**:93, 1942.

219. Lewis, P. J., and Low, J. H.: Amebiasis in Yakima Valley, Northwest Med. **41**:52, 1942.

220. Most, H., and Helpern, M.: Incidence of Trichinosis in New York City, Am. J. M. Sc. **202**:251, 1941.

Wyrens, Tillisch and Magath [221] add still another report to those already extant. Theirs is of interest for the fact that in 21 of 40 cases mentioned the diagnosis was made incidentally during routine examination of surgical pathologic material, the parasites being found in specimens of muscle removed from various parts of the body, in tonsillar and in thyroid tissue and in tissue removed from the lips. In the other 19 cases clinical trichinosis was present.

The treatment of various parasitic diseases is well considered in the newer textbooks on the subjects. An excellent summary, however, is presented in adequate detail and in convenient form by Faust [222] in an article entitled "The Chemotherapy of Intestinal Parasites," in which he discusses the most recent and successful forms of treatment. The author takes up in order the use of emetine, chiniofon powder, diodoquin (5,7-diiodo-8-hydroxyquinoline) and carbarsone in the treatment of amebiasis, atabrine in giardiasis and gentian violet in infections caused by Oxyuris and Strongyloides; hexylresorcinol is advocated in the treatment of ascariasis; for hookworm infection the author routinely uses tetrachlorethylene and (or) hexylresorcinol; for infection caused by whipworm no specific drug therapy is available, but the use of fresh crude latex and the repeated administration of tetrachlorethylene are mentioned; infection caused by tapeworm may be treated successfully either by oleoresin of aspidium or by carbon tetrachloride. The article is written in enough detail that it is highly informative. Manson-Bahr [223] believes that the most effective treatment for amebiasis is a combined method of therapy, consisting of quinoxyl (a mixture of iodohydroxyquinoline sulfonic acid and bicarbonate of soda) retention enemas by day and administration of emetine bismuth iodide by night. Using this method, the author had a relapse rate of only 3.7 per cent in 361 patients. Kuitunen-Ekbaum [224] has found that phenothiazine is extremely efficacious in the treatment of infection caused by pinworm and claims complete cures in 84 of 98 cases by the first course of treatment. Although it is generally recognized that giardiasis may be successfully treated by atabrine, there is still a reasonably skeptical attitude toward the relation that infections caused by Giardia bear to the production of symptoms. For this reason, it is of some interest to learn from an article by Hartman

221. Wyrens, R. G.; Tillisch, J. H., and Magath, T. B.: Trichinosis: Report of Nineteen Cases of Clinical Infection and Twenty-One Cases of Asymptomatic Infection, J. A. M. A. **117**:428 (Aug. 9) 1941.

222. Faust, E. C.: Chemotherapy of Intestinal Parasities, J. A. M. A. **117**: 1331 (Oct. 18) 1941.

223. Manson-Bahr, P.: Amebic Dysentery and Its Effective Treatment; Critical Study of Five Hundred and Thirty-Five Cases, Brit. M. J. **2**:255, 1941.

224. Kuitunen-Ekbaum, E.: Phenothiazine in the Treatment of Enterobiasis, Canad. Pub. Health J. **32**:308, 1941.

and Kyser [225] that apparently atabrine therapy completely relieved the rather indefinite symptoms presented by a group of patients in whom the demonstration of giardias in the intestine was the only positive clinical finding.

Specific Infections, Diagnosis and Treatment.—An apparently unique case of multiple subserous abscesses in a single locality of the stomach wall is described by Sauer and Lisa.[226] The report is mentioned, in spite of the fact that the causation remained obscure, because there appears to be no report of a similar condition in the literature. Histologic studies revealed chronic gastritis and multiple acute subserous abscesses.

Infections caused by Welch's bacillus have rarely given rise to serious lesions in the stomach and the duodenum. Only 12 cases were found in the literature by Quinn and his colleagues.[227] They add 2 new cases, in which localized infection due solely to Welch's bacillus was encountered in the stomach and the duodenum. Recovery was reported in only 1 case.

Because of the increasing tendency to segregate patients suffering from tuberculosis in special institutions it is an unfortunate fact that younger physicians are becoming less familiar with the various manifestations of this disease. For this reason reference to current articles should be of interest. Burke and Aronovitch [228] comment on the incidence of ulcerative intestinal tuberculosis encountered among patients in a sanatorium. Of 99 consecutive autopsies, ulcerative lesions in the digestive tract were encountered in 70 per cent. Over a period of fourteen months 226 patients in the same institution revealed an incidence of intestinal tuberculosis of 31.4 per cent when examined by a method previously described by Brown and Sampson. Because of the histories of dietary inadequacy obtained from a large number of these patients, vitamin therapy was instituted in the hospital, with particular attention to vitamins C and D. It is the authors' impression that there has been a marked decrease in the number of patients presenting symptoms referable to the intestinal tract since the beginning of such therapy. It would be of interest to know whether during this period patients with less advanced tuberculous conditions were being admitted than in former years. Such a possibility might in part explain the apparent improvement in therapeutic results. It is of incidental interest that in children, at any rate,

225. Hartman, H. R., and Kyser, F. A.: Giardiasis and Its Treatment, J. A. M. A. **116**:2835 (June 28) 1941.

226. Sauer, P. K., and Lisa, J. R.: Abscess of the Stomach Wall: Report of a Case, Surgery **10**:899, 1941.

227. Quinn, W. C.; Lord, J. W., Jr., and Wade, L. J.: Welch Bacillus Infections Arising from the Stomach and Duodenum, Surgery **11**:229, 1942.

228. Burke, H. E., and Aronovitch, M.: Intestinal Tuberculosis, Canad. M. A. J. **45**:21, 1941.

gastric lavage may be an important procedure in the diagnosis of tuberculosis. Davies and Doherty [229] surveyed the results of examination of gastric contents in 75 boys and girls ranging from 2 to 11 years of age. Of this group, 64 children had pulmonary tuberculosis and 11 had nonpulmonary lesions. Tubercle bacilli of the type causing tuberculosis in human beings were present in the gastric contents of 24 of the patients with pulmonary tuberculosis but not in those of any children suffering from nonpulmonary lesions. Although such a maneuver is rarely necessary or indicated in adults, it undoubtedly is occasionally indicated in children, in whom the obtaining of satisfactory specimens of sputum is often difficult. The possible importance of abdominal tuberculosis in causing symptoms in children leading to erroneous diagnoses is stressed in an article by Harrenstein.[230] Under the term abdominal tuberculosis this author includes involvement of the peritoneum and tuberculosis of the mesenteric lymph nodes and of the abdominal organs. The slight cutaneous sensitivity to tuberculin of patients with these conditions increases the diagnostic difficulties. In 47 of 48 children the cause of symptoms was established only by operation. The first diagnosis for the majority of the children had been erroneous, the tuberculous process being frequently mistaken for appendicitis. In 20 children active tuberculosis of the lymphatic nodes was encountered; in 23 tuberculous peritonitis was encountered, and in 5 intestinal lesions were suspected. Because of the probability of an increase in the morbidity from tuberculosis due to war or postwar conditions, articles on this disease are of current interest.

A rather unusual manifestation of early syphilis of the stomach is reported by Reynolds,[231] who relates the case of a 34 year old Negro with pyloric obstruction. The patient was found to have a chronic interstitial inflammatory lesion of the wall of the stomach associated with early syphilis. That the syphilitic infection was recent seemed clear because of the presence of a penile lesion and a characteristic plantar syphilid with generalized lymphadenopathy. That the gastric lesion was also due to syphilis seemed entirely probable because of the suggestive histopathologic data and the response to specific treatment. Another rare manifestation of syphilis of the digestive tract is to be found in a case report of Hernández-Morales and Ruiz-Cestero,[232] who describe a case

229. Davies, T. W., and Doherty, C. J.: Gastric Lavage in Diagnosis of Tuberculosis in Children: Survey of Seventy-Five Cases, Brit. M. J. **1**:212, 1942.

230. Harrenstein, R. J.: Abdominal Tuberculosis in Children, Maandschr. v. kindergeneesk. **9**:442, 1940.

231. Reynolds, F. W.: Gastric Lesions Associated with Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **26**:218, 1942.

232. Hernández-Morales, F., and Ruiz-Cestero, G.: Syphilis of the Duodenum, Am. J. Digest. Dis. **8**:302, 1941.

in which an obstructing lesion in the second portion of the duodenum responded slowly to antisyphilitic treatment; there was also serologic evidence of the disease. Proof of healing was obtained by repeated roentgen examination, as well as by the disappearance of symptoms.

Actinomycosis of the gastrointestinal tract is sufficiently rare to warrant including a report by Woodman [233] of a case in which the condition was diagnosed at operation. Involvement of the cecum, ascending colon and liver was demonstrated, in addition to multiple small pulmonary abscesses.

Recent improvements in the diagnosis and treatment of bacillary dysentery are of immediate interest because of the obviously increased exposure to this infection of a large number of American troops and civilians moving to different parts of the world. The fairly recent development of a culture medium selective for Bacillus dysenteriae (Flexner) is reported by Wilson and Blair.[234] They have found that lactose nutrient agar containing optimum amounts of potassium tellurite, potassium ferric iron and rosolic acid provides a medium on which Flexner's organisms grow profusely, whereas the growth of most strains of Escherichia coli and Bacillus lactis aerogenes is inhibited. The growth of salmonellas which cause food poisoning, typhoid and paratyphoid bacilli, Sonne's dysentery bacillus and cholera vibrios is suppressed. A careful clinicopathologic study of 263 consecutive cases of acute bacillary dysentery observed in the Canal Zone is presented by Macumber.[235] The organisms recovered from stools consisted entirely of members of the Flexner and the Sonne group, those of the former predominating heavily. No case of infection with Shiga's bacillus was encountered. By means of control cases Macumber concludes that no evidence could be obtained indicating that polyvalent serum therapy was of value. The mortality for the entire series was 6.5 per cent, relatively more deaths being due to infections caused by Sonne's bacillus. Careful microscopic studies were made of the pathologic material obtained in 13 cases. The results of these are given in detail. This report is of particular interest inasmuch as the mortality figures are based on the results of treatment before the use of chemotherapeutic agents. A report from the Netherlands East Indies is of interest. Esseveld and his colleagues [236] studied 64 cases of mild

233. Woodman, T. W.: Abdominal Actinomycosis, Southwestern Med. **25**: 81, 1941.

234. Wilson, W. J., and Blair, E. M. M.: Tellurite-Iron Rosolic Acid Medium Selective for Bacillus Dysenteriae (Flexner), Brit. M. J. **2**:501, 1941.

235. Macumber, H. H.: Acute Bacillary Dysentery: A Clinicopathologic Study of Two Hundred and Sixty-Three Consecutive Cases, Arch. Int. Med. **69**: 624 (April) 1942.

236. Esseveld, H.; Beau, W., and Boars, J. K.: Bacteria of Newcastle Dysentery Group from Feces of Patients with Symptomatology and Bacillary Dysentery in Netherlands East Indies, Geneesk. tijdschr. v. Nederl.-Indië **81**:2622, 1941.

dysentery on the east coast of Sumatra. The feces yielded a bacterial strain of the Manchester type of the Newcastle dysentery organisms. Simultaneous bacteriologic tests on the feces from patients without dysentery never disclosed this strain. A report from Germany by Roelcke and Neuberger[237] was received in 1941 in which the authors maintained that the Kruse-Sonne form of dysentery has shown a considerable increase in the past ten years. Infection caused by Shiga-Kruse bacilli was never detected, and the authors claim that in recent years Kruse-Sonne bacilli account for over 85 per cent of all cases of dysentery in Germany. The highest incidence was observed in children under 10 years of age and occurred during the summer months. Kruse-Sonne dysentery occurred as frequently as infection caused by paratyphoid B organisms. A most unusual clinical manifestation of bacillary dysentery is described in a report by Thorne and Estabrook.[238] A major outbreak of diarrheal disease and infectious jaundice occurred in a Vermont state school, an institution with a capacity of three hundred and eighty beds. During a ten month period there were three distinct phases, which occurred as follows: Thirty-two patients showed symptoms of dysentery alone during the first phase of the epidemic; 26 patients showed dysentery and jaundice later, and subsequently 62 patients presented jaundice alone. Flexner's organisms were demonstrated in 50 patients having dysentery alone, in 2 patients presenting dysentery and jaundice together and in 5 patients presenting jaundice alone. The organisms were also found in 14 symptom-free carriers and were demonstrable in stool specimens intermittently for weeks or months after the end of the acute epidemic. The authors are careful to avoid drawing any conclusions as to the relation between the jaundice and the infection with dysentery bacilli, which were probably introduced by a symptom-free carrier and spread by improperly disinfected clothing passing through a central laundry.

Therapeutic measures to be considered in the treatment of bacillary dysentery at present include serum therapy and the use of bacteriophages and various chemotherapeutic agents. A comment has already been made on what appear to be carefully controlled reports following the use of polyvalent antiserum. The use of dysentery bacteriophages is discussed by Klieve and Helmreich[239] and by Soesman.[240] The former article

237. Roelcke, K., and Neuberger, M.: Statistics on Kruse-Sonne (E) Dysentery: The Infectious Intestinal Disease Most Prevalent in Germany, München. med. Wchnschr. **88**:643, 1941.

238. Thorne, F. C., and Estabrook, J. S.: The Association of Bacillary Dysentery and Infectious Jaundice, J. A. M. A. **117**:89 (July 12) 1941.

239. Klieve, H., and Helmreich, W.: Dysentery Bacteriophages, München. med. Wchnschr. **88**:617, 1941.

240. Soesman, J.: Polybacteriophage in Treatment of Bacillary Dysentery, Geneesk. tijdschr. v. Nederl.-Indië **81**:1863, 1941.

reports the results obtained by German physicians in Poland. These authors believe that opinions about the value of bacteriophages in the treatment of dysentery are divided because the bacteriophages differ in efficacy. It has been found that not only the bacilli vary in different epidemics and endemic foci but probably the bacteriophages. In Poland the authors observed that local strains of bacteriophage produced lysis in all strains of dysentery bacilli obtained locally, whereas bacteriophages brought in from Germany did not. They believe it highly important to use a potent polyvalent mixture produced from locally obtained strains. The prophylactic value of their bacteriophage mixture was tested, and it was noted that in the course of eight weeks following the administration of the mixture, dysentery developed in 10 of 250 controls, whereas not a single man of the 113 who had received prophylactic treatment had the disease. During the course of an epidemic it was proved that bacteriophage therapy was effective in cases of mild or moderately severe infection caused by Flexner Y organisms. The treatment was not so effective in the cases of most severe infection. It is of interest that apparently the administration of bacteriophage was successful in the treatment of carriers. Similar results appear to have been obtained by Soesman, who treated 50 patients with bacillary dysentery with polyvalent bacteriophage during an epidemic in the Netherlands East Indies. The author considered that in most instances severe symptoms disappeared more rapidly than in untreated patients. All of the patients in this group recovered.

The use of sulfonamide compounds in the treatment of intestinal infections was to have been expected and has already been productive of important results. Of the various preparations, sulfaguanidine (sulfanilylguanidine) has received the most attention, inasmuch as it was hoped originally that the action of this drug would be largely confined to the intestinal tract. According to the original report of Marshall and his collaborators (1940), the drug in mice and dogs is poorly absorbed from the intestinal tract, and subsequent studies by Corwin [241] substantiate this result in the case of dogs and monkeys. A species difference definitely exists, however, and later reports indicate that an appreciable amount of the drug is absorbed in human beings and may, at times, produce toxic symptoms. Such a discrepancy is noted, for example, in the report of Beling and Abel,[242] who demonstrated urinary excretion of sulfaguanidine by human beings in amounts ranging from 29 to 66 per cent of a total ingested dose with the exception of 1 subject who excreted 96 per cent of the drug. The authors are agreed that the compound is effective in reducing the total number of colon bacilli in the stools,

241. Corwin, W. C.: Studies on the Chronic Toxicity of Sulfaguanidine (Sulfanilylguanidine), Bull. Johns Hopkins Hosp. **69**:39, 1941.

242. Beling, C. A., and Abel, A. R.: Sulfaguanidine: Absorption, Excretion and Therapy, J. M. Soc. New Jersey **38**:629, 1941.

although the growth of anaerobic bacteria is not influenced. Corwin, among others, noted that the drug did not cause a decrease in the total number of organisms, although it caused a marked suppression of gram-negative bacilli and permitted a concomitant increase in gram-positive cocci. In animal experiments Bloomfield and Lew [243] showed that the drug, even when administered in small doses, had a striking prophylactic effect against the spontaneous development of ulcerative cecitis in rats, at the same time preventing any loss of weight, although the disease developed in untreated rats and the animals showed evidence of profound nutritional disturbances. These authors suggest the trial of this or similar drugs as a prophylactic measure in military establishments. Comparative studies on the effects of sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), sulfathiazole (2-[para-aminobenzenesulfonamido]-thiazole) and sulfaguanidine were made by Lawrence and Sprague,[244] who used these drugs to determine in animals their effect against colon-typhoid-dysentery organisms. Feeding the several compounds in the diet to mice caused with a single exception a significant reduction in the number of coliform organisms normally present in the intestinal contents; sulfanilamide apparently had no effect. From Mexico comes a report by Aquilar [245] on the use of sulfapyridine in the treatment of mucosanguineous colitis. This author reports excellent results following the administration of sulfapyridine in some 200 cases. Keeley and McCord [246] investigated the absorption of sulfaguanidine from the colon after administering it through well functioning colostomy openings. The authors conclude that the drug in the form of an aqueous suspension when introduced directly into the large bowel through a colostomy stoma is not absorbed from the left half of the colon in human beings.

The therapeutic trial of sulfonamide compounds in acute intestinal infections is reported by various writers. Valdès and Sosa-Gallardo [247] employed sulfathiazole in the treatment of 43 children with bacillary dysentery (17 with Shiga dysentery, 6 with Flexner dysentery and 20

243. Bloomfield, A. L., and Lew, W.: Prophylactic Effect of Sulfaguanidine Against Ulcerative Cecitis in Rats, Proc. Soc. Exper. Biol. & Med. **48**:363, 1941.

244. Lawrence, C. A., and Sprague, K. D.: Effects of Sulfanilamide, Sulfapyridine, Sulfathiazole and Sulfanilylguanidine upon Colon-Typhoid-Dysentery Group, Proc. Soc. Exper. Biol. & Med. **48**:696, 1941.

245. Aquilar, R.: Sulfapyridine in Therapy of Mucosanguineous Colitis, Rev. méd. d. Hosp. gen. **3**:504, 1941.

246. Keeley, J. L., and McCord, W. M.: Concentration of Sulfaguanidine (Sulfanilylguanidine) in the Peripheral Blood of Human Beings After Its Introduction into the Large Bowel and After Oral Administration, J. Lab. & Clin. Med. **27**:785, 1942.

247. Valdès, J. M., and Sosa-Gallardo, J. B.: Treatment of Bacillary Dysentery with Sulfathiazole, Arch. argent. de pediat. **17**:3, 1942.

with Sonne dysentery). There were no deaths, and tenesmus, colic and other disturbances disappeared within six to eight hours after ingestion of the drug. The number of evacuations decreased and became normal before seventy-two hours had elapsed. The authors gained the impression that infectious diarrhea which proved refractory to sulfathiazole should be considered of nondysenteric origin. A report from Cooper and his associates [248] presents the results of sulfathiazole treatment of acute diarrhea in 123 infants and children. An analysis of the results showed that the drug was of therapeutic value in patients whose stools were positive for Shigella paradysenteriae but was without demonstrable effect in the treatment of patients whose stools were negative for this organism. The data indicated that sulfathiazole hastened the disappearance of S. paradysenteriae from the stools of the treated patients. Seventeen of 34 patients who did not receive sulfathiazole had cultures of stools which were positive for these organisms on discharge from the hospital, while only 1 of 17 patients treated with the drug had cultures which were thus positive at the time of discharge. A careful control experiment was carried out by Anderson, Cruickshank and Walker,[249] who administered sulfaguanidine to alternate patients suffering from attacks of Flexner dysentery. Of the total of 96 patients, 41 received the drug and 55 were untreated controls. The results on the drug-treated patients were excellent. In a case of typical severe dysentery thus treated the patient's condition improved in twenty-four hours after receiving the drug, and by the thirteenth day practically all symptoms had disappeared. Bowel movements were much less frequent within two days, although blood and mucus often persisted in the stools for three or four days. Convalescence was much shorter than in the untreated patients, and treatment with the drug in the acute stage apparently prevented the convalescent carrier state, which was present in about half of the untreated patients. A smaller but similar control experiment was carried out by Hall [250] on 30 patients suffering from dysentery due without exception to Hiss Y bacilli. Of the 30 patients, all but 5 were infants or children. The results on the drug-treated patients were excellent, and all but 2 had a dramatic response in about twenty-four hours. In the control group the course of the disease followed that which had been observed in the past, and there was 1 death. In the same report the authors record the effects of a similar course of treatment in

248. Cooper, M. L.; Zucker, R. L., and Wagoner, S., with statistical analysis by Brown, E. W., and Bennett, R.: Sulfathiazole for Acute Diarrhea and Dysentery of Infants and Children, J. A. M. A. **117**:1520 (Nov. 1) 1941.

249. Anderson, D. E. W.; Cruickshank, R., and Walker, J.: Treatment of Bacillary (Flexner) Dysentery with Sulfanilylguanidine, Brit. M. J. **2**:497, 1941.

250. Hall, L. C.: The Use of Sulfaguanidine in Enteric Infections, J. Pediat. **20**:328, 1942.

5 patients with infection caused by typhoid organisms. In this group apparently the drug was completely ineffective, a result which has been observed by all other investigators. Of particular importance in the present war emergency is the report of Rantz and Kirby,[251] who observed the results following sulfaguanidine therapy in the treatment of dysentery carriers. Eleven carriers, picked up in a recent survey in San Francisco, were treated with an average dose of 50 Gm. administered over two to six days. In 9 of the 11 persons dysentery bacilli disappeared from the stools during treatment and could not be demonstrated in subsequent periods of study varying from thirty to ninety days. In 2 instances the treatment appeared to be ineffective even after three courses of therapy. It is important to note that all of the patients remained ambulatory and continued to work while being treated.

The newest member of the sulfonamide compounds to be utilized in the treatment of intestinal infection is sulfasuxidine (succinylsulfathiazole). Thorough pharmacologic studies by Miller and associates[252] have demonstrated that succinylsulfathiazole administered orally to dogs has little toxicity; that it is poorly absorbed from the intestinal tract, so that only an average of about 5 per cent or less of the ingested drug is excreted by the kidneys; that its action is essentially in the intestinal tract, affecting principally the contents of the bowel; that it has a marked effect in altering the bacterial flora, as demonstrated by the reduction in the count of E. coli and related organisms, and that in therapeutic doses it profoundly alters the feces, which become semifluid and practically odorless. It has also been observed that dysentery bacilli, including Shiga, Flexner and Sonne strains, are susceptible to its antibacterial action, and the fact that the feces become relatively odorless indicates marked inhibition of anaerobic proteolytic bacteria. Reports by Poth and his collaborators[253] form the basis for such conclusions. These authors have used as a preliminary working dose in human beings 0.25 Gm. per kilogram per day administered orally. They

251. Rantz, L. A., and Kirby, W. M. M.: The Use of Sulfaguanidine in the Treatment of Dysentery Carriers, J. A. M. A. **118**:1268 (April 11) 1942.

252. Miller, E.; Rock, H. J., and Moore, M. L.: Substituted Sulfanilamide: I. N^4-Acyl Derivative, J. Am. Chem. Soc. **61**:1198, 1939. Moore, M. L.; Miller, C. S., and Miller, E.: Substituted Sulfanilamide: II. N^4-Acyl-N^1-Hydroxyl Derivative, ibid. **62**:2097, 1940. Moore, M. L., and Miller, C. S.: Dicarboxylic Acid Derivatives of Sulfonamide, ibid. **64**:1572, 1942.

253. Poth, E. J.; Knotts, F. L.; Lee, J. T., and Inui, F.: Bacteriostatic Properties of Sulfanilamide and Some of Its Derivatives: I. Succinylsulfathiazole, a New Clinicotherapeutic Agent Locally Active in the Gastrointestinal Tract, Arch. Surg. **44**:187 (Feb.) 1942. Poth, E. J., and Knotts, F. L.: Clinical Use of Succinylsulfathiazole, ibid. **44**:208 (Feb.) 1942; Succinyl Sulfathiazole: A New Bacteriostatic Agent Locally Active in the Gastro-Intestinal Tract, Proc. Soc. Exper. Biol. & Med. **48**:129, 1941.

have found that there is a significant lowering of the coliform organisms in 90 per cent of instances after the administration of the drug in adequate doses. The medication has been effective in the presence of extensive ulcerating lesions of the bowel, and they suggest the administration of succinylsulfathiazole for the preoperative preparation of patients requiring surgical procedures on the gastrointestinal tract and for the treatment of acute intestinal infections, such as typhoid fever and dysentery. All the evidence at hand seems to indicate that the action of the drug is limited essentially to its local effect on the contents of the gastrointestinal tract. Such has been the experience of various investigators, including my own. From unpublished data it appears that the drug is of no value in the treatment of typhoid fever, as is shown by Kirby and Rantz.[254] These authors administered the drug to normal persons and to typhoid and to dysentery carriers, and the results are compared to those following the administration of sulfaguanidine. Succinylsulfathiazole was given to 11 persons in the dose suggested by Poth and associates in the articles just referred to. Three of the subjects were apparently normal; 3 were typhoid carriers, and 5 were dysentery carriers. Although the drug produced a decided alteration of physical characteristics in the bacterial flora of the stools, typhoid bacilli remained viable in the stools of the 3 carriers during two weeks of drug therapy. In the case of dysentery carriers the bacilli disappeared from the stools during the administration of the drug and remained absent for periods varying from thirty to sixty days. It would appear that this new drug, which is now available, offers a distinct advantage in the treatment of many acute intestinal infections, particularly those due to the dysentery-like bacilli. Further reports on its effectiveness should receive careful scrutiny. Because of the minimal amount of absorption from the gastrointestinal tract, its use should be associated with few toxic symptoms, and for this reason it should prove preferable to sulfaguanidine.

The treatment of lymphogranuloma venereum by sulfonamide compounds is considered by Palmer, Kirsner and Rodaniche.[255] In addition to an excellent discussion of the disease in the clinical and the subclinical form, the authors present their impression of the results of chemotherapy. They believe that treatment with sulfanilamide and sulfaguanidine is of definite value, particularly in those cases in which there is no stricture formation, but warn that prolonged administration of the drugs may

254. Kirby, W. M. M., and Rantz, L. A.: The Treatment of Typhoid and Dysentery Carriers with Succinylsulfathiazole, J. A. M. A. **119**:615 (June 20) 1942.

255. Palmer, W. L.; Kirsner, J. B., and Rodaniche, E. C.: Studies on Lymphogranuloma Venereum Infection of the Rectum, J. A. M. A. **118**:517 (Feb. 14) 1942.

be necessary. On the basis of experimental and clinical evidence they conclude that the sulfonamide compounds are unable to destroy all the virus in the body but that they do tend to inhibit its action. Six patients suffering from proctitis due to lymphogranuloma venereum were treated with sulfaguanidine by Cañizares and Morris.[256] Their results coincided with the impressions gained by Palmer and his associates. Those patients with simple inflammatory proctitis experienced subjective and objective improvement, which was not noted in the patients with narrow fibrotic strictures. Such a result is not surprising and serves to indicate the wisdom of early diagnosis and treatment of this not uncommon condition before rectal strictures develop.

Continued studies reveal the great importance of stools as a source of infection in poliomyelitis. One of the latest reports is that of McClure,[257] who was able to obtain five "takes" after inoculation of monkeys with material obtained from stools of 17 patients with typical, abortive or atypical suspected poliomyelitis. All of the successful passages were from stools of infants under 2 years of age. No answer has yet been obtained to the question as to what conditions are necessary for the poliomyelitis virus to remain infectious in stools. As a public health measure the subject warrants prolonged and thorough investigation.

A rather unusual report having to do with the bacterial flora of the intestinal tract is contained in an article by Bergeim and his colleagues,[258] who noted that there was a 57 per cent recovery of Bacillus prodigiosus from the large intestine in man when such bacteria were ingested with a given amount of olive oil. Only 11 per cent recovery was obtained when the bacteria were ingested with butter fat and less than 2 per cent when taken with an equal amount of an alcoholic extract of butter fat with a higher butyrate content. Concentrations of butyric acid inhibiting growth or killing bacteria at different p_H values are reported for about twenty organisms, including many which occur normally or pathologically in the intestine. Such studies may indicate a further method of possible therapeutic control of the intestinal flora. In a somewhat similar form of study Portis and Fishbein[259] noted that

256 Cañizares, O., and Morris, G. E.: Sulfaguanidine in Treatment of Proctitis Due to Lymphogranuloma Venereum: Report of Six Cases, Arch. Dermat. & Syph. **44**:873 (Dec.) 1941.

257. McClure, G. Y.: High Incidence of Infective Stools in a Small Outbreak of Infantile Paralysis, J. Lab. & Clin. Med. **27**:1906, 1941.

258. Bergeim, O.; Hanszen, A. H.; Pincussen, L., and Weiss, E.: Relation of Volatile Fatty Acids and Hydrogen Sulphide to the Intestinal Flora, J. Infect. Dis. **69**:155, 1941.

259. Portis, S. A., and Fishbein, W. I.: Studies of Feces and Clinical Conditions Following Ingestion of Grape Juice, Illinois M. J. **80**:336, 1941.

the ingestion of 24 ounces (720 cc.) of grape juice daily increased the number of gram-positive organisms in the stools in a consistent fashion, along with the acidophilus bacilli. The effect of the continued use of this preparation in 50 persons who tended to complain of chronic constipation was striking. No laxatives were needed throughout the course of the experiment.

An excellent example of an epidemiologic study of an outbreak of food poisoning is given by Kleeman and his associates.[260] Two cases of food poisoning were found to be due to smoked fish, the source of which was eventually traced and eradicated. Samples of the food gave high counts of Proteus vulgaris. The principal importance of the article lies in the attention that it draws to the hazards concerned in the distribution of perishable foods, such as fish.

An explanation of the favorable effect of pectin on infectious diarrheas caused by intestinal pathogens is the subject of a report by Werch and associates[261] following studies on various intestinal pathogens, such as the typhoid-dysentery group. The authors present evidence, which seems reasonably convincing, that pectin, galacturonic acid and their decomposition products manifest bactericidal, as well as bacteriostatic, activity. They believe that the influence of pectin on the p_H of the intestinal contents is the most probable explanation of its antibacterial activity.

Regional Enteritis.—Although the cause of regional enteritis still remains an unknown quantity, continued clinical investigations bring into clearer relief the various manifestations of this unusual disease. A report by Wirts and Lyon[262] on 71 cases encountered at six teaching hospitals in Philadelphia constitutes a satisfactory summary of clinical knowledge of the condition at the present time. In all cases the patients had been operated on. Of 27 considered to have the advanced form of the disease, one third had had appendectomies at an average time of twenty months prior to the major operation. The remaining 44 patients were considered to have had an early form of the disease, and the majority in this group before operation had conditions given the diagnosis of acute appendicitis. A resemblance to the last-named disorder seems to be one of the most typical characteristics of the condition, and

260. Kleeman, I.; Frant, S., and Abrahamson, A. E.: Food Poisoning Outbreaks Involving Smoked Fish: Their Epidemiology and Control, Am. J. Pub. Health **32**:151, 1942.

261. Werch, S. C.; Jung, R. W.; Plenk, H.; Day, A. A., and Ivy, A. C.: Pectin and Galacturonic Acid and the Intestinal Pathogens, Am. J. Dis. Child. **63**:839 (May) 1942.

262. Wirts, C. W., Jr., and Lyon, B. B. V.: The Incidence of Regional Ileitis, Am. J. Digest. Dis. **8**:246, 1941.

the confusion in diagnosis illustrates the difficulty with which the early stages of the condition are recognized. The authors have collected 17 other cases, in which the evidence was not sufficiently complete to warrant an absolute diagnosis of regional enteritis. In these cases the patients were not operated on, although the diagnosis was reasonably certain on the basis of signs, symptoms and laboratory studies. Partial or complete relief of symptoms in this group was obtained in essentially one half of the patients, who were maintained on a medical regimen. The authors conclude that it is highly probable that the early form of the disease does not necessarily progress to the advanced state. Certainly, a review of the available literature indicates that in a fair number of patients immediate radical surgical intervention is not warranted, even in the presence of an adequate diagnosis and that conservative measures are still justified in the absence of any exact knowledge as to the cause of the disease. Such conservative measures, however, are justified only in those instances in which it is possible to maintain a constant watch over the individual patient. Brown and Donald,[263] on the contrary, believe that in every case surgical removal of the diseased segment of bowel is indicated, and there can be no doubt that the characteristic course of the condition, with its remissions and exacerbations similar to those encountered among patients with peptic ulcer and chronic ulcerative colitis, cannot be forgotten. In the report of these authors on 178 patients one again finds an excellent summary of the present information concerning the disease, including comments on its incidence, the distribution of its lesions and its progress. One important therapeutic note in this report is the statement by Brown and Donald that the most important feature in the postoperative care of the condition is the maintenance of a high protein diet which is supplemented with the vitamin B complex. There can be no doubt that this is a most important consideration, and too frequently the necessity of carrying out careful nutritional therapy after the removal of an appreciable amount of the absorptive surface of the small bowel is not observed, with resulting disability and occasionally the development of serious nutritional disorders.

It is not too common to encounter massive hemorrhage in association with regional enteritis. Fallis[264] reports 1 case of such an occurrence, the only one in a group of 27 patients in whom operation was performed because of repeated and profuse intestinal bleeding. The condition was not suspected until a laparotomy was performed.

263. Brown, P. W., and Donald, D. J., Jr.: Prognosis of Regional Enteritis, Am. J. Digest. Dis. **9**:87, 1942.

264. Fallis, L. S.: Massive Intestinal Hemorrhage in Regional Enteritis: Report of a Case, Am. J. Surg. **53**:512, 1941.

One set of experiments by Poppe [265] has more or less succeeded in reproducing some of the features of enteritis and is quite similar to some other experiments carried out within recent years. In dogs the author was able to produce acute and chronic enteritis, with some additional involvement of the colonic mucosa, by obstructing the lymphatic drainage of the ileocecal segment of the intestine. Ulcerating lesions could be produced without the injection of any bacteria, but the injection of nonpathogenic bacteria into the mesenteric lymph nodes appeared to produce acute, generalized enteritis, rather than the chronic ulcerating form. Such experiments suggest the possible mechanism underlying the production of regional enteritis but unfortunately do not contribute any definite evidence of its causation.

Nonspecific Ulcerative Colitis.—The question of the causation, diagnosis and treatment of chronic ulcerative colitis continues to be the basis of investigation and speculation. Various diagnostic methods are well discussed by Paulson.[266] In his critical analysis of the various procedures he stresses the need for complete studies, including a search for specific micro-organisms, parasites and viruses. The seriousness of ulcerative colitis is such that a perusal of Paulson's article is worth while, largely because it presents all of the various aids that may be utilized from time to time in evaluating a given case.

The frequency with which this disease may be encountered in young children is not generally recognized. For this reason the report by Elitzak and Widerman [267] should be mentioned. Twenty-seven patients were observed in an age group ranging from two weeks upward. Eight of the patients died, and most of the fatalities occurred in infants under the age of 1 year, the duration of the disease in these patients varying from six days to one year. In 5 of the surviving patients the disease showed no symptoms of activity for a long time and the lesions seemed to be healed. In spite of this small group of cases of apparently arrested disease the authors properly point out that the prognosis must be guarded because of the characteristic tendency toward relapses and recurrences. Occasional instances are reported of a familial occurrence of the condition. Jackman [268] in a review of 900 cases found that less than 2 per

265. Poppe, J. K.: Reproduction of Ulcerative Colitis in Dogs, Arch. Surg. **43**:551 (Oct.) 1941.

266. Paulson, M.: Diagnostic Methods in Chronic Ulcerative Colitis: A Critical Analysis of Procedures Used in the Differential Diagnosis of the Diarrheas and Dysenteries, Am. J. Clin. Path. **11**:588, 1941.

267. Elitzak, J., and Widerman, A. H.: Nonspecific Ulcerative Colitis in Childhood, Am. J. Dis. Child. **62**:115 (July) 1941.

268. Jackman, R. J.: Familial Occurrence of Chronic Ulcerative Colitis (Thrombo-Ulcerative Colitis): Report of Case, Proc. Staff Meet., Mayo Clin. **17**:154, 1942.

cent were encountered in which 2 or more members of a family had the disease. Detailed reports are given by him on 2 families, which are of some interest. In the first family 2 young brothers reported that the disease became evident at the same time, almost to the day, sixteen months prior to examination by a physician. The results of sigmoidoscopic and roentgen examination of the 2 patients were almost identical. In a second family 3 young members were involved by a severe process which ended fatally.

The close relation between certain aspects of ulcerative colitis and psychologic disturbances is fairly generally recognized. Daniels [269] in a careful psychiatric study of 25 persons suffering from the disease comes to what is usually the accepted conclusion—that except for the basic factors relating emotions to disturbances of the large intestine, the psychophysiologic mechanism of ulcerative colitis is not understood. He does make one important observation, which should be clear to all physicians familiar with the variations in the disease, namely, that recurrences may bear a significant relation to emotional disorders and at times the symptoms mask a severe depression. He also points out the fact still too infrequently considered that in many instances there is a direct relation between the severity of the physical reaction of the disease and the underlying psychopathologic condition.

The relation between ulcerative colitis and allergic disturbances is also fairly well recognized. Many observers are convinced that it is not a primary allergic phenomenon but that allergic manifestations are important complications of the condition. Andresen,[270] however, is convinced that in a large proportion of patients suffering from ulcerative colitis the disease develops solely on the basis of abnormal sensitivity to food allergens. He regards the resemblance between the mucosal lesions of ulcerative colitis and allergic reactions of the skin as quite obvious. The results obtained by Andresen in a series of 50 cases cannot be ignored and undoubtedly reflect the excellent care which the patients received. The article, however, is not convincing as a demonstration of the origin of the condition. Nevertheless, the details involved in the treatment outlined by this author should be read with care and should form the basis of helpful therapy in many instances.

The complications encountered in the course of ulcerative colitis are known and have been frequently described by Bargen and others, but the number of patients with this disease encountered by the average physician in practice is relatively small. For this reason it is quite proper

269. Daniels, G. E.: Psychiatric Aspects of Ulcerative Colitis, New England J. Med. **226**:178, 1942.

270. Andresen, A. F. R.: Ulcerative Colitis—An Allergic Phenomenon, Am. J. Digest. Dis. **9**:91, 1942.

in a review of this sort to mention periodically some of the less usual manifestations of the condition. One of the not too uncommon complications is associated arthritis, which can usually be properly classified as rheumatoid in nature. As has been pointed out by other authors, the activity of the arthritic process is apt to coincide with exacerbations of the colitis, and favorable results following colectomy, as far as the course of the arthritis is concerned, are usually to be expected. Presumably, in such instances the colon actually behaves as a focus of infection. One such instance is adequately described by Wright.[271] Bargen's contribution to knowledge of the clinical manifestations of the disease has been outstanding. In a recent note,[272] he calls attention to a most unusual complication, namely, nephrolithiasis. In all 6 cases reported by the author renal stones apparently developed some years after a permanent ileostomy had been performed. In 4 instances the renal calculi were bilateral, and in each instance infection of the urinary tract was present. It is of incidental interest that in 3 cases the patients suffered from frequent attacks of arthritis. The mechanism underlying the formation of such calculi is not clear and might well form the basis of careful studies on the metabolism of calcium and phosphorus in ileostomized subjects. A further report by Hopping and Bargen [273] describes the condition as a disease of complications, and in addition to mentioning personal difficulties, also notes the exhibition of other conditions, such as arthritis, cardiac disease, iritis, erythema nodosum and nephritis. Another not infrequent clinical manifestation associated with chronic ulcerating disease of the colon is that of cutaneous changes. Felsen [274] reports 3 instances of a rather unusual type of cutaneous manifestation complicating this disease. In each case during an exacerbation of the colitis multiple areas of cutaneous necrosis, generally discrete but sometimes confluent, appeared. The lesions started as small, painful, reddened papules, in which subsequently developed a central zone of necrosis and ulceration. In all of the lesions the floor of the ulcer was formed by muscle or fascia. Besides the rapidly necrotizing character of the lesions, two striking features were the depth and the extension of the subcutaneous involvement. Cultures of material from the lesions revealed the presence of E. coli, Staphylococcus aureus and nonhemolytic strepto-

271. Wright, A. D.: Ulcerative Colitis Complicated by Polyarthritis Treated by Total Colectomy, Proc. Roy. Soc. Med. **25**:189, 1942.

272. Bargen, J. A.: Nephrolithiasis Complicating Ulcerative Colitis After Ileostomy: A Report of Six Cases, J. Urol. **46**:183, 1941.

273. Hopping, R. A., and Bargen, J. A.: Cases of Chronic Ulcerative Colitis Encountered at the Clinic in 1939, Proc. Staff Meet., Mayo Clin. **17**:151, 1942.

274. Felsen, J.: Multiple Necrotizing Skin Lesions in Chronic Ulcerative Colitis, New York State J. Med. **41**:2228, 1941.

cocci; no anaerobic organisms were found. Elsom and his colleagues [275] call attention to a phenomenon already pointed out by Mackie that is of particular interest in cases of complicated ulcerative colitis. In 7 ileostomized patients nitrogen balance studies were carried out, and it was shown that the nitrogen excretion in the ileal discharge was abnormally great in 4 of them. This finding is entirely in keeping with the frequent demonstration of transient changes in the terminal portion of the ileum suggesting an actual disease process. As these authors point out, however, roentgen and clinical evidence of ileal involvement practically always disappears coincident with clinical improvement of the underlying colitis, and it is highly probable that it is a nutritional disturbance, rather than any actual inflammatory disease of the small intestine.

The etiologic role of "Bacterium necrophorum" in ulcerative colitis has been studied for some time by Dragstedt and his collaborators.[276] A summary of the work, with a discussion of the complicating factors, is of interest but leaves one with a good deal of doubt as to the final significance of the results. Similarly, a clinical study by Henderson, Pinkerton and Moore [277] concerning "Histoplasma capsulatum" as a cause of the disease is to be mentioned.

Therapeutic measures that apparently have been efficacious in the hands of different investigators are numerous. Whether one agrees with the specificity of the measures employed, it is of interest to mention them in the hope that subsequent experience will make it possible to evaluate their importance. Winkelstein and Shwartzman [278] claim that they obtained marked improvement in 20 of 29 patients with nonspecific ulcerative colitis after the use of a concentrated and purified antitoxic E. coli serum. Weiss, Slanger and Goodfriend [279] believe that they have observed excellent results following the use of mixed vaccines prepared from cultures of material taken from the nose, throat and rectosigmoid

275. Elsom, K. A.; Dickey, F. G., and Chornock, F. W.: Functional Disturbances of the Small Intestine in Chronic Idiopathic Ulcerative Colitis, Am. J. Digest. Dis. **9**:74, 1942.

276. Dragstedt, L. R.; Dack, G. M., and Kirsner, J. B.: Chronic Ulcerative Colitis: A Summary of Evidence Implicating Bacterium Necrophorum as an Etiologic Agent, Ann. Surg. **114**:653, 1941.

277. Henderson, R. G.; Pinkerton, H., and Moore, L. T.: Histoplasma Capsulatum as a Cause of Chronic Ulcerative Enteritis, J. A. M. A. **118**:885 (March 14) 1942.

278. Winkelstein, A., and Shwartzman, G.: The Use of Concentrated and Purified Antitoxic B. Coli Serum in the Treatment of Indeterminate Ulcerative Colitis, Am. J. Digest. Dis. **9**:133, 1942.

279. Weiss, S.; Slanger, A., and Goodfriend, S.: The Relation of the Nasopharynx to Ulcerative Colitis, J. Lab. & Clin. Med. **27**:1925, 1941.

mucosa. Obviously, no specificity can be claimed for such a measure. Streicher [280] has observed the results following the use of azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate) and sulfathiazole and has come to the conclusion that little or no improvement is obtained by the use of these preparations, except in cases of mild disease. He is of the opinion that medical treatment for the most part is indicated in this disease and limits the use of ileostomy, with or without colectomy, to those patients in whom the colon has undergone irreparable change. Recent reports on sulfonamide therapy have to do principally with the use of sulfaguanidine. Kirsner and his associates [281] conclude that the use of this drug in chronic, nonspecific ulcerative colitis has not yet yielded any striking therapeutic results. Variable results were obtained by Stickney, Heilman, Bargen and Dearing [282] on a group of 46 patients. They also feel that it is impossible to state with any degree of certainty that the drug is responsible for the favorable response obtained in some of their patients. Many failures were observed, and they feel that the exact place of sulfaguanidine in the progress of the therapy of ulcerating intestinal disease has not been established. In view of previous favorable reports the article by Shiffer and Ferguson [283] regarding the use of a concentrated liver extract and vitamin B_1 is of interest. These authors consider that these medications have contributed nothing to the treatment of this disease, except possibly from the point of view of replacement.

Parenthetically, it will not be amiss to stress again the striking manifestations of deficiency disease so frequently noted as a secondary manifestation of prolonged diarrhea. Frequent attention has been called to this circumstance, and the necessity for replacement therapy cannot be too strongly emphasized. Additional articles mentioning such manifestations have been presented recently by Molina,[284] Diaz y Rivera,[285]

280. Streicher, M. H.: Chronic Ulcerative Colitis: A Clinical Summary of the Management in Nine Hundred and Twelve Cases, J. A. M. A. **118**:431 (Feb. 7) 1942.

281. Kirsner, J. B.; Rodaniche, E. C., and Palmer, W. L.: Use of Sulfaguanidine in Nonspecific Ulcerative Colitis and Other Infections of the Bowel, Proc. Inst. Med. Chicago **14**:53, 1942.

282. Stickney, J. M.; Heilman, F. R.; Bargen, J. A., and Dearing, W. H.: Sulfaguanidine in Ulcerative Intestinal Disease, Proc. Staff Meet., Mayo Clin. **17**:33, 1942.

283. Shiffer, P., and Ferguson, L. K.: The Treatment of Idiopathic Ulcerative Colitis with Concentrated Liver Extract and Vitamin B_1, Am. J. Digest. Dis. **8**:300, 1941.

284. Molina, R. R.: Sprue in Puerto Rico: A Clinical Study of One Hundred Cases, Puerto Rico J. Pub. Health & Trop. Med. **17**:134, 1941.

285. Diaz y Rivera, R. S.: The Prothrombin Time in Tropical Sprue, Puerto Rico J. Pub. Health & Trop. Med. **17**:124, 1941.

Oettel and Thaddea [286] and Bercovitz.[287] These articles deal with manifestations of avitaminosis A and B_1, prolongation of prothrombin time, hypoproteinemia and avitaminosis C, respectively.

Appraisal of medical versus surgical therapeutic measures is still difficult. The complications following ileostomy and colectomy, as previously indicated, should not be ignored. There can be little doubt that there is a real place for radical surgical intervention in this condition, but as a rule its undertaking is unwise unless adequate medical measures have failed to control the situation. In many instances medical measures suffice to maintain a patient in relatively good health, but it seems proper to point out that maintenance of life alone by medical means is not a justification for the continuation of medical treatment. Once a patient with ulcerative colitis fails to maintain himself as a useful, ambulatory individual, it is important to recognize that medical therapy has failed and that an indication exists for proper surgical intervention. Perusal of the articles by Reed and Rochex,[288] Elsom and Ferguson [289] and Cave and Thompson [290] should prove worth while, as they all contain interesting discussions of this moot question.

Cancer of the Colon and the Rectum.—Examples of malignant lesions occurring in early life continue to multiply. Kennedy,[291] Oosting,[292] Laird [293] and Pennell and Martin [294] report the occurrence of such malignant manifestations in infants and children. The report of Kennedy is particularly pertinent inasmuch as he records 49 cases of rectal and colonic polyps in infants and children. The patients ranged in age from 6 months to 13 years, and the lesions were visualized by proctoscopic or

286. Oettel, H., and Thaddea, S.: Hypoproteinemia in Nontropical Sprue, Deutsches Arch. f. klin. Med. **187**:353, 1941.

287. Bercovitz, Z.: Recent Advances in the Treatment of Chronic Ulcerative Colitis, M. Clin. North America **24**:683, 1940.

288. Reed, A. C., and Rochex, F.: Treatment of Chronic Ulcerative Colitis Based on Thirty Cases, Northwest Med. **40**:332, 1941.

289. Elsom, K. A., and Ferguson, L. K.: Appraisal of Medical Versus Surgical Treatment of Idiopathic Ulcerative Colitis: Follow-Up Data on Fifty Cases, Am. J. M. Sc. **202**:59, 1941.

290. Cave, H. W., and Thompson, J. E.: Mortality Factors in the Surgical Treatment of Ulcerative Colitis, Ann. Surg. **114**:46, 1941.

291. Kennedy, R. L. J.: Polyps of the Rectum and Colon in Infants and in Children, Am. J. Dis. Child. **62**:481 (Sept.) 1941.

292. Oosting, M.: Adenocarcinoma of the Sigmoid Colon, Rectum, and Anus in Children: Report of Two Cases in a Thirteen-Year Old Girl and an Eight-Year-Old Boy with Summary of Recorded Cases up to Fifteen Years of Age, Ohio State M. J. **37**:1067, 1941.

293. Laird, T. K.: Carcinoma of the Colon in a Child of Fourteen Years with a Review of the Literature, Am. J. Surg. **53**:335, 1941.

294. Pennell, V., and Martin, L. C.: Carcinoma of the Colon in Children with Report of a Case, Brit. J. Surg. **29**:228, 1941.

roentgen examination. The hereditary character of polypoid disease of the colon is mentioned, as well as the tendency to malignant degeneration.

A critical commentary on the tardiness with which rectal cancer is diagnosed is made by Braund and Binkley [295] on the basis of 108 unselected patients. The facts presented are not new but deserve comment. Symptoms had been present for an average period of eight to ten months before the patients sought medical advice. Of 100 patients the disease was diagnosed without undue delay in only 25 after they were referred to a physician. For the remaining 75 there was an additional average delay of between nine and ten months, during which time they received inadequate and improper therapy. Twenty patients had not had a rectal examination, although more than 90 per cent of rectal cancers were within reach of the examining finger. Thirty-seven had been examined digitally but improperly, with the result that no mass was detected before the patients were referred to the clinic. Forty-six of the 100 patients saw between two and five physicians before being referred for a final diagnosis. In the face of such facts, which unfortunately are not unusual, it is small wonder that the early diagnosis of cancer still leaves much to be desired.

Unlike cancer of the stomach, recognition of metastases in the presence of cancer of the colon and the rectum seems to be readily accomplished by the exploring surgeon, as shown in a study by Mayo and Schlicke.[296] In those cases in which death occurred shortly after resection, no metastases were encountered at necropsy in more than four fifths of those cases in which none was found at operation. Residual cancer was encountered in only 5 per cent of the cases in which death occurred shortly after resection. An important comment is made by these authors when they state that in their opinion independent growths are frequently responsible for many "recurrences." For this reason, they suggest that whenever a carcinoma is encountered in any portion of the colon or the rectum, the presence of a second carcinoma must be carefully ruled out. A study by Coller, Kay and MacIntyre [297] similar to the one already reviewed [154] on regional lymphatic metastases of carcinoma of the stomach by the same authors is presented in relation to the colon. Here again, a large number of specimens of cancer of the colon were carefully studied, with a minute examination of the regional

295. Braund, R. R., and Binkley, G. E.: Plea for Earlier Diagnosis of Rectal Cancer: Analysis of One Hundred and Eight Clinic Patients, New York State J. Med. **42**:33, 1942.

296. Mayo, C. W., and Schlicke, C. P.: Carcinoma of the Colon and Rectum: A Study of Metastasis and Recurrences, Surg., Gynec. & Obst. **74**:83, 1942.

297. Coller, F. A.; Kay, E. B., and MacIntyre, R. S.: Regional Lymphatic Metastases of Carcinoma of the Colon, Ann. Surg. **114**:56, 1941.

lymph nodes. An average of 52 nodes were isolated in each specimen and were examined for metastatic involvement. Two thirds of the specimens showed such involvement. There was no essential difference in the spread noted in carcinoma of the right half and of the left half of the colon. As a careful anatomic study this report should be read by all surgeons. An unusual association of rectal cancer is mentioned by Nordlander,[298] who reports a group of cases in which primary cancer was encountered simultaneously in the uterus and in the rectum.

Because of the frequent occurrence of cancer of the rectum an article by Bowling and Dixon [299] on advances in the treatment of this disease is significant and encouraging. One important comment on therapy lies in the statement that electrosurgery, or actual cauterization, radium therapy and roentgen therapy are not competitive measures but are decidedly complementary in nature. Reason for the hope that early diagnosis of carcinomatous lesions of the colon and the rectum will be associated with successful therapy is illustrated in the statistics presented by Bargen and his collaborators.[300] Of 61 patients on whom operations were performed for carcinomatous lesions less than 2.5 cm. in diameter (in other words, early lesions), 28 were living at the end of five years and 24 at the end of seven years. It is of incidental interest to note that in 47 of the 61 patients the lesions were located within easy reach of the examining finger or of a sigmoidoscope, an indication of the necessity for early examination.

Previous mention has been made of carcinoid tumors, most of which occur in the appendix. Waugh and Snyder [301] mention that only 11 carcinoid tumors of the colon have been reported, in 5 of which the lesion was in the cecum. The authors report 1 additional case, in which the cecum was involved.

Although admitting that it is generally held that radical surgical intervention is the measure of choice in the treatment of multiple polyposis of the colon, Vanzant [302] recommends the employment of roentgen therapy. He reports 2 cases in which the condition appeared to respond favorably to irradiation. Whether such a measure is justifiable remains

298. Nordlander, E.: Primary Cancer in the Uterus and in the Rectum of the Same Patient, Acta radiol. **22**:439, 1941.

299. Bowling, H. H., and Dixon, C. F.: Advances in the Treatment of Carcinoma of the Rectum, M. Clin. North America **25**:915, 1941.

300. Bargen, J. A.; Cromar, C. D. L., and Dixon, C. F.: Early Carcinoma of the Colon: I. Nature and Adequate Treatment of the Small Carcinoma, Arch. Surg. **43**:186 (Aug.) 1941.

301. Waugh, J. M., and Snyder, J. M.: Carcinoid Tumor of the Cecum, Ann. Surg. **114**:151, 1941.

302. Vanzant, B. T.: Roentgen Therapy in Hereditary Diffuse Polyposis of the Colon, J. A. M. A. **118**:875 (March 14) 1942.

open to some question, but there can be little doubt that irradiation therapy of cancer of the rectum is at times justified. Such treatment probably should be used only as a palliative measure, however, and the results of irradiation are carefully presented by Sharp.[303] In addition, he records apparently favorable results, with eradication of the growth by irradiation, in 13 patients who were followed up for four to eight years. This group received high voltage roentgen therapy to skin tolerance combined with implantation of seeds.

Cases of malignant growth of the anus are not too frequent. For this reason the report by Lawrence[304] of 2 instances of basal cell epithelioma of the anus are worthy of comment. Apparently, only 4 cases have been previously reported.

Appendicitis.—The causes leading to acute appendicitis are still not entirely understood. For this reason the study by Dennis[305] on the physiologic behavior of the appendix in human beings and the problem of appendicitis is of more than academic interest. This author attempted experiments on 272 excised appendixes in order to determine the contractility and the resistance to flow through the lumen of the organ. Evidence is presented that acute, suppurative appendicitis, but not gangrene, may be initiated by spasm of the portion of the muscle wall of the appendix, although the stimulus for this spasm is not known. The author found that inflamed appendixes presented an average resistance to outflow of fluid through the appendix into the cecum which was twice that observed in normal specimens. Figures obtained on "interval" specimens fell between these two values. Appendical pain, Dennis believes, including the pain radiating to the right lower quadrant of the abdomen, is largely due to tension on the muscular wall of the organ and may be ameliorated by epinephrine. He states that seepage of infected fluid through the appendical wall occurs at levels of intraluminal tension commonly reached in appendicitis, and he offers this as an explanation of many cases of peritonitis without rupture. Rupture of the organ during an acute attack he believes to be due to digestion of the wall, inasmuch as the normal appendical wall can withstand an intraluminal tension of 2 atmospheres. Completely obstructed appendixes, he believes, may remain uninflamed because of loss of the secretory power of the mucosa.

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303. Sharp, G. S.: The Radiation Treatment of Cancer of the Rectum: Technique for Radium Needles Through Perineal Stab Wounds, Am. J. Roentgenol. **46**:207, 1941.

304. Lawrence, K. B.: Basal Cell Epithelioma of the Anus: Report of Two Cases, Arch. Surg. **43**:88 (July) 1941.

305. Dennis, C.: Physiologic Behavior of the Human Appendix and the Problem of Appendicitis, Arch. Surg. **43**:1021 (Dec.) 1941.

The relation between oxyuriasis and appendicitis continues to attract attention, and reports by Schwarz and Straub,[306] Morehead[307] and Ashburn[308] attest to the frequency with which this association is encountered. Of extreme importance is the report of Straus[309] on 2 cases in which infectious mononucleosis simulated accute appendicitis. It is not generally recognized that this infectious disease may at times be associated with fulminating attacks of abdominal pain. That such may be the case is illustrated by Straus's report. In 1 case atypical hyperplasia of the lymphoid tissue of the appendix was described, which was identical with the lesions encountered in the lymph glands of patients with infectious mononucleosis. Inasmuch as this disease is characterized by typical changes in the blood smear, it is important to emphasize the necessity of careful examinations of the blood in cases of acute conditions in the abdomen before resorting to surgical procedures.

The frequency of occurrence of acute appendicitis is illustrated in a statistical report by Petrén,[310] who describes the incidence of this condition in southwestern Sweden and refers to a similar statistical study by Quensel. According to these authors, it would appear that if one takes the life span as a whole, 12.5 per cent of the total population could be expected to have acute appendicitis. The mortality from appendicitis still remains reasonably high due to lack of public education and too long a delay between the onset of symptoms and proper operative procedures. The improper use of laxatives undoubtedly continues to be a contributing cause. An unusual comment is made by Jennings and his associates,[311] who suggest that the factor of fatigue on the part of the operating room team, the surgeon and the patient may be of importance in bringing about the death of the patient. They suggest that after admission to the hospital and diagnosis, night operations be avoided in the absence of signs of spreading peritonitis, in order to overcome the aforementioned factor and to adjust the frequently disturbed electrolyte balance of the patient. These authors, in conjunction with many others, strongly recommend

306. Schwarz, J., and Straub, M.: Oxyuriasis and Appendicitis, Arch. Path. **33**:28 (Jan.) 1942.

307. Morehead, R. P.: The Pinworm and the Appendix, North Carolina M. J. **2**:349, 1941.

308. Ashburn, L. L.: Appendiceal Oxyuriasis: Its Incidence and Relationship to Appendicitis, Am. J. Path. **17**:841, 1941.

309. Straus, R.: Infectious Mononucleosis Simulating Acute Appendicitis with Description of a Specific Lesion of the Appendix, Am. J. Clin. Path. **12**: 295, 1942.

310. Petrén, G.: Question of Frequency of Acute Appendicitis, Chirurg **13**: 236, 1941.

311. Jennings, J. E.; Burger, H. H., and Jacobi, M.: Acute Appendicitis: A Clinical and Pathologic Study of 1,680 Consecutive Cases, Arch. Surg. **44**:896 (May) 1942.

the wider use of the McBurney incision. The use of sulfanilamide powder in the wound has cut down minor complications in the absence of drainage and has permitted a tighter closure of the incision when drainage has been used. Its intraperitoneal use may be beneficial in early peritonitis, according to Deaver.[312] Taylor and Hodges [313] believe that it contributes little once peritonitis has developed. In a frank discussion of the causes of death from acute appendicitis Aud [314] courageously states that some lives might have been saved by more careful preoperative examination and preparation, a better selection of time for operation, a different type of operation and more intensive and better postoperative treatment. He deplores the frequent lack of adequate operative notes and postoperative records and is properly impressed by the fact that in 90 per cent of deaths in a certain area, no autopsies had been done to determine the exact cause of death. A plea for more general education of the public as a means of preventing deaths from this condition is made by Cutler and Hoerr,[315] who state that in their series the mortality rate from acute appendicitis remains the same as it did twenty-five years ago, in spite of advance in surgical technic. Hill and Fellman [316] also insist on the fatal consequences of delay in diagnosis. In over one fifth of the fatal cases in their series of over 1,000 the patients received purgatives, although the authors believe that this does not necessarily mean that the purgatives caused the deaths. They suggest the probability that the important factor was the delay occasioned by the patients staying at home and receiving family care with familiar household remedies for some time before consulting a physician. Education of the community and of the medical profession appears to have produced favorable results according to the report given by Carraway.[317] This author believes that the reduction in the mortality in his series is due in part to the following factors: a correct taking of history and careful physical examination, permitting an early diagnosis; insistence that the family physician does not procrastinate and that if in doubt he procure a competent consultant, and assignment of patients with peritonitis to only the most thoroughly trained and experienced surgeons.

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312. Deaver, J. M.: Acute Appendicitis in Children, Pennsylvania M. J. **45**: 358, 1942.

313. Taylor, E. S., and Hodges, R. G.: Acute Appendicitis in Children, Surg., Gynec. & Obst. **73**:288, 1941.

314. Aud, G.: Deaths from Acute Appendicitis in Louisville, South. M. J. **34**:914, 1941.

315. Cutler, E. C., and Hoerr, S. O.: Acute Appendicitis: Twenty-Five-Year Study, J. Michigan M. Soc. **41**:203, 1942.

316. Hill, G. C., and Fellman, A. C.: Acute Appendicitis: A Study of 1006 Consecutive Cases, Nebraska M. J. **26**:359, 1941.

317. Carraway, C. N.: Management of Patients with Appendicitis with Special Reference to Those with Perforation, J. Alabama M. A. **11**:91, 1941.

An excellent statistical study of 671 cases of appendical peritonitis is given by Rogers and Faxon.[318] In the absence of a palpable mass the authors urge the use of a clinical basis for the appraisal of each individual case and feel that the success of treatment will be determined by ability to recognize in advance those cases in which localization of peritoneal infection will or will not take place and ability to select the safest time for operation, together with good preoperative and postoperative care. The greatest mortality was noted in those patients who looked ill on admission and were operated on more than six hours after an incident interpreted as acute perforation. This appearance of being very ill they believe to be the most unfavorable prognostic sign; absence of active peristalsis they believe is next in importance, and a pulse rate too rapid for the white cell count is the most unfavorable laboratory finding. From a study of 227 cases in which a mass was palpable they conclude that operation should rarely be done under such circumstances on the fifth, the sixth or the seventh day of illness and that incision and drainage alone should be carried out. Appendectomy should be performed within six weeks of this procedure. They are firmly convinced that even when a localized lesion has formed, the general clinical impression that the patient presents at entry, of being very ill or not very ill, is of more reliable prognostic significance than any laboratory data.

An interesting laboratory observation is reported by Lesser and Kaufman.[319] In 99 cases of acute appendicitis in which the diagnosis was confirmed by operation, blood sedimentation rates were normal. In 33 additional cases in which patients with conditions given a preoperative diagnosis of acute appendicitis were operated on, elevated sedimentation rates were obtained. In 18 of these cases complicating appendical abscesses or general peritonitis of varying degree was presented; in 15 cases, the diagnosis of appendicitis was erroneous and extra-appendical conditions were encountered. The authors would seem to be justified in concluding that in an abdominal condition simulating acute appendicitis, the finding of an abnormally high sedimentation rate should indicate either a serious complication or extra-appendical disease.

The question of chronic appendicitis is a hardy perennial. Warren and Ballantine [320] record the results of appendectomy for recurrent pain

318. Rogers, H., and Faxon, H. H.: A Statistical Study of Six Hundred and Seventy-One Cases of Appendiceal Peritonitis: I, New England J. Med. **226**: 707, 1942. Faxon, H. H., and Rogers, H.: A Statistical Study of Six Hundred and Seventy-One Cases of Appendiceal Peritonitis: II, ibid. **226**:745, 1942.

319. Lesser, A., and Kaufman, L. R.: Five Year Survey of Blood Sedimentation Test in Acute Appendicitis, Surg., Gynec. & Obst. **73**:163, 1941.

320. Warren, R., and Ballantine, H. T., Jr.: Chronic Appendicitis: Results After Appendectomy for Recurrent Pain in Right Lower Quadrant of the Abdomen, J. A. M. A. **117**:994 (Sept. 20) 1941.

in the right lower quadrant of the abdomen. Of a series of 138 cases in which an inflamed appendix was removed, the operative specimen in 49 showed typical "chronic appendicitis" on histologic examination. Of the entire group, in about three fourths partial or complete relief of preoperative symptoms was experienced, but the authors take pains to point out that in those cases in which there were long histories or numerous attacks the percentage of good end results was not so high as in those in which there were short histories or few attacks. They admit that the mortality from the operation is low but rightfully state that the morbidity and the period of incapacity following operation cannot be ignored. For this reason they urge the adoption of a more conservative attitude toward operative procedures for chronic appendicitis.

Clarke and Shapiro [321] comment on 3 cases of acute appendicitis in which pain was not the first symptom. Such a clinical observation is of real importance. In 1 instance a shaking chill preceded the onset of pain by several hours; in a second, malaise and vomiting were the initial symptoms and lasted for some time, and in a third case, the appearance of pain was preceded by seventeen hours of malaise, fainting and vomiting. The necessity of an accurate physical diagnosis in the presence of such atypical pictures is obvious.

From the foregoing comments and reports, it would seem imperative that members of the medical profession in this country take the matter of appendicitis even more seriously than at present and increase their efforts to educate not only the public but other members of their profession as to the proper moves to be made in the treatment of this dangerous condition.

Miscellaneous Observations.—An unusual type of observation is that reported by Paine and Nessa [322] on the distribution and transport of gas in the gastrointestinal tract of infants and young children. Roentgenograms of the abdomen were made on 46 children, varying in age from a few minutes to 10 years. All of these infants and children were thought to have normally functioning digestive tracts. It was found that up to 18 months of age gas was distributed equally between the small bowel and the colon, between 18 months and 6 years of age more and more intestinal gas was located in the colon and less in the small bowel and after 7 years of age, as in adulthood, no gas was normally present in the small bowel. Serial roentgenograms of the abdomen were made on 7 newborn infants. In each case gas was observed to be already

321. Clarke, R., and Shapiro, M.: Pain in Acute Appendicitis, Lancet **2**:39, 1941.

322. Paine, J. R., and Nessa, C. B.: Observations on the Distribution and Transport of Gas in the Gastrointestinal Tract of Infants and Young Children, Surgery **11**:281, 1942.

present in the stomach, duodenum or jejunum by the time the first roentgenogram could be taken, as soon as possible after birth, which was within six to fifteen minutes and within four to six hours after birth gas was present in the sigmoid flexure of the colon or the rectum.

An unusual form of injury to the gastrointestinal tract is discussed by Poer and Woliver.[323] They comment on the problem of subparietal intestinal injury due to nonpenetrating abdominal trauma. A study of a large series of cases revealed the interesting fact that a relatively high percentage of injuries was due to a relatively small variety of accidents, which included injuries due to personal encounters, in which the patient was struck or kicked in the abdomen or fell on it; the results of industrial accidents caused by blunt objects, and accidents concerned with transportation, frequently with motion at a high rate of speed. Distention of the intestine with fluid or with food contributed to the likelihood of rupture, as was evidenced by the fact that many injuries were received soon after the patients had eaten. The necessity for early intervention is stressed. Duodenal rupture with fat necrosis but without evident pancreatic injury is a rare abdominal condition following trauma. Two cases of such a condition are reported by Dixon.[324]

A more general recognition of the dangers inherent in heavy radiation to the intestinal tract or to neighboring structures is apparent from recent articles. Warren and Friedman [325] provide an excellent discussion of the pathology and pathologic diagnosis of radiation lesions in the gastrointestinal tract, which should be of interest not only to the pathologist but to the internist. This is particularly true since a determination on pathologic grounds as to whether a given lesion is entirely or in part due to irradiation may have importance for further therapy. Thirty-eight cases were selected for study, including ulcers, fistulas and strictures which developed at sites distant from neoplastic tissue subjected to irradiation or at the site of a partially or completely destroyed tumor. The bowel wall was usually thickened and indurated, with an opaque serosa, and telangiectasia was prominent. Similar involvement was frequently noted in the adjacent mesentery. The mucosa of the bowel rarely appeared entirely normal, but usually, even in the nonulcerated lesions, atrophy and fixation to the submucosa were seen. The degree of ulceration ranged from confluent, superficial erosions to deep, punched-out ulcers. Stenosis was sometimes due to diffuse sclerosis

323. Poer, D. H., and Woliver, E.: Intestinal and Mesenteric Injury Due to Non-Penetrating Abdominal Trauma, J. A. M. A. **118**:11 (Jan. 3) 1942.

324. Dixon, G. G.: Duodenal Rupture and Fat Necrosis: Report of Two Cases, Ann. Surg. **114**:147, 1941.

325. Warren, S., and Friedman, N. B.: Pathology and Pathologic Diagnosis of Radiation Lesions in the Gastro-Intestinal Tract, Am. J. Path. **18**:499, 1942.

with general constriction of a segment and sometimes to formation of a stricture at a site of ulceration. Necrosis was part of most reactions, and in extreme instances the reaction approached massive gangrene. The necessity of a knowledge of the existence of such lesions should be obvious to those interested in irradiation therapy. Experimental observations were made by the same authors [326] on the evolution of radiation ulcers of the intestine. The observations were made on rabbits, which received a course of irradiation totaling 4,000 r distributed in eight to ten doses given approximately every other day. Lesions of the bowel developed slowly, and ulcerations became more marked during the second and the third month after therapy. The histologic findings are of interest but do not warrant detailed discussion. These two articles, with reference to previous work, such as that done by Engelstad (1938) and Ferguson (1938), represent a real contribution. A somewhat related series of observations is to be found in an article by K'o, Tu and Chan.[327] These authors were interested in the possibly unfavorable effects that might occur during the administration of iron while patients were undergoing irradiation therapy. Experiments were made on dogs, and it was found that ferrous sulfate was definitely valuable in the treatment of anemia as a result of chronic blood loss and caused no harmful effects while the animals were undergoing abdominal irradiation. When ferrous citrate was given in therapeutic doses under similar circumstances, gross intestinal lesions occurred. The lesions noted appeared to be similar to those described by Warren and Friedman.

Megacolon has received a certain amount of attention during the past year. Etzel [328] goes so far as to raise the question whether the disease complex that includes megaesophagus, megacolon and megaureter, may be caused by chronic vitamin B_1 deficiency. The paper is based on a study of 170 cases, with pathologic studies on 16 autopsy specimens, encountered in the region of São Paulo, Brazil. Degeneration in the intramural autonomic nervous system is believed to be the anatomic basis for these manifestations, and the author has attempted to link this with the evidence of a vitamin B_1 deficiency believed to be due to the dietary habits of the local population. The article is far from convincing, but the subject matter presented offers the basis for interesting speculations. A different concept of the possible relation between disorders of

326. Friedman, N. B., and Warren, S.: Evolution of Experimental Radiation Ulcers of the Intestine, Arch. Path. **33**:326 (March) 1942.

327. K'o, Y. K.; Tu, C. L., and Chan, B. C.: The Effect of Hard Roentgen Rays on Intestines of Normal Dogs Fed on Inorganic Iron Compounds, Surg., Gynec. & Obst. **73**:333, 1941.

328. Etzel, E.: May the Disease Complex That Includes Mega-Esophagus (Cardiospasm), Megacolon and Mega-Ureter Be Caused by Chronic Vitamin B_1 Deficiency? Am. J. M. Sc. **203**:87, 1942.

the nervous system and megacolon is presented by Vidal,[329] who believes that hypothalamic disturbances may be of some etiologic importance in this condition. This investigator destroyed in rats the medial preoptic area and the lateral hypothalamus and adjacent areas by means of a unipolar electrode and observed after several weeks the development of megacolon. In a discussion of the therapeutic measures applicable to congenital megacolon, Soper [330] considers that sympathectomy should be discarded. He bases such an opinion on a review of the literature and his own personal observations, particularly in 1 case, in which presacral sympathectomy was followed by a marked reduction in the size of the colon but at the same time permitted a volvulus to occur from the markedly lengthened mesentery of the small bowel. Prior to the development of this acute condition in the abdomen uncontrollable diarrhea had been present as an aftermath of the operative procedure. He believes that resection of the colon, according to Dixon's method, should be employed in all cases, with the possible exception of those in which the patient is suffering from a severe form of malnutrition. In these cases he advocates the performance of an ileostomy, with subsequent colectomy as an elective procedure. He records the experiences of 12 patients who have been treated by such a radical procedure.

Kantor,[331] as usual, contributes an observation of interest in the description of what he terms the "diaphragmatic flexure." By this term he describes a splenic flexure which is located directly under the left side of the diaphragm and which he was able to demonstrate in about 15 per cent of almost 1,000 patients studied. It is often associated with a redundant colon. This anatomic anomaly is associated with symptoms only when other conditions exist, such as the presence of gas due to colonic malfunction. When symptoms do occur in connection with this condition, Kantor points out that the most important ones are those associated with the production of heartburn, thoracic distress and cardiac embarrassment. The colonic origin of heartburn has heretofore been overlooked and is accordingly emphasized. Kantor states that the thoracic symptoms occur whether or not organic heart disease is present. Appropriate therapeutic measures obviously must include those calculated to bring about effective colonic evacuation. The importance of the article lies in the fact that here is another possible source of confusion in the interpretation of symptoms relating to the possible existence of heart

329. Vidal, F.: Hypothalamus and Megacolon, Arch. argent. de enferm. d. ap. digest. y de la nutrición **17**:310, 1941-1942.

330. Soper, H. W.: Megacolon, Am. J. Roentgenol. **46**:655, 1941.

331. Kantor, J. L.: Colon Studies: VIII. The Diaphragmatic Flexure, Am. J. Roentgenol. **4**:417, 1942.

disease. I am in entire accord with the suggestions made by the author, and my attention has been called to such a possible source of "cardiac symptoms" by Dr. T. R. Harrison. The exact mechanism underlying the production of such symptoms, however, is not at all clear and should be studied.

An unusual occurrence is that noted by Lemman and Paschal,[332] who report a case of rupture of the stomach following the ingestion of sodium bicarbonate. They record 31 cases of spontaneous rupture of the stomach reported in the literature. In this particular instance, the accident followed the ingestion of a large amount of food and alcohol, following which the patient took bicarbonate of soda in generous doses for relief of abdominal fulness.

An unusual source of food poisoning is reported by Frant and Irving [333] and may be of some importance. These authors report five outbreaks of food poisoning due to cadmium, involving at least 50 persons. The syndrome was characterized by violent acute gastritis, occurring almost immediately after the ingestion of contaminated food. The cadmium responsible for the outbreak was found in liquids and in food preparations which had come in contact with cadmium-plated utensils. The cadmium metallic coating on the utensils was found to be soluble when placed in contact with solutions of dilute acetic acid and other organic acids commonly found in foods. Resulting organic cadmium salts were formed, which when taken internally produced poisonous cadmium chloride when combined with the hydrochloric acid of the gastric juice. It would seem highly important that the plating industry be made cognizant of the fact that cadmium is not a suitable substance for the plating of utensils used for food.

The possible harmful effects of karaya gum and other bulky materials frequently used therapeutically were investigated by Hoelzel, DaCosta and Carlson.[334] These investigators cite the results of previous experiments by Ivy and Isaacs, who reported an absence of intestinal lesions in albino rats fed 1 Gm. of karaya gum daily for ninety-one days. In the present study a large number of animals were given somewhat larger doses of the gum for a longer period. Hooded rats appeared to be more susceptible than albino rats to the development of lesions of the lower portion of the bowel. Serious intestinal lesions were encountered in 3 of 5 hooded rats who were fed large amounts of karaya gum for long

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332. Lemman, W. T., and Paschal, G. W., Jr.: Rupture of the Stomach Following Ingestion of Sodium Bicarbonate, Ann. Surg. **114**:997, 1941.

333. Frant, S., and Irving, K.: Cadmium "Food Poisoning," J. A. M. A. **117**:86 (July 12) 1941.

334. Hoelzel, F.; DaCosta, E., and Carlson, A. J.: Production of Intestinal Lesions by Feeding Karaya Gum and Other Materials to Rats, Am. J. Digest. Dis. **8**:266, 1941.

periods. The animals were fed diets which included granular karaya gum, bran or a poor grade of psyllium seed. Whether such results can be applied to the use of these substances in human beings remains to be seen. Fantus and his associates [335] have attempted to prove that bran has no harmful effect in human beings and provide a series of reports on this subject. Numerous stool examinations were first carried out to obtain some measure of colonic irritability, particularly on the basis of the content of mucus and leukocytes. Bran when added to an uncontrolled diet appeared to cause a softening and an increase in the weight of the stools. There was an increase in the volatile fatty acids, chiefly acetic and butyric acids, but there appeared to be no consistent correlation between this change and the laxative action associated with the ingestion of bran. The authors conclude that no conclusive evidence exists that bran causes or increases irritation of the bowel. The stool abnormalities which were occasionally noted, due to an increase in mucus, were attributed to other causes. A reasonable criticism of such conclusions seems proper. All of the experiments were made on healthy persons with no complaints referable to the bowel. The use of bran as a therapeutic agent has long been advocated as a corrective measure in patients with bowel disorders commonly known as "constipation." There can be no doubt that in many such instances, in patients with "irritable colon," "mucous colitis," etc., in whom constipation is a common clinical feature, the use of bran frequently causes an aggravation of existing symptoms.

Morgan [336] adds his protest against the use of liquid petrolatum to those of certain other investigators. According to this author, liquid petrolatum frequently causes symptoms, such as anorexia, indigestion, flatulence, fatigue, nervousness, dyschesia and anal leakage. In addition, he refers to the fact that it seriously interferes with the utilization of carotene, vitamin A concentrates and fat-soluble vitamin D. Such an indictment of a popular remedy is probably justified in part, although it is to be doubted that under ordinary conditions effects really deleterious to the health of the patient are encountered after its use.

As an unusual and curious observation the article by Felsen [337] on the sigmoidoscopic diagnosis of periarteritis nodosa should be mentioned.

335. Fantus, B.; Wozasek, O., and Steigmann, F.: Studies on Colon Irritation: Examination of Feces, Am. J. Digest. Dis. **8**:296, 1941. Fantus, B., and Frankl, W.: The Mode of Action of Bran: I. Effect of Bran upon Composition of Stools, J. Lab. & Clin. Med. **26**:1774, 1941. Fantus, B.; Wozasek, O., and Steigmann, F.: Studies on Colon Irritation: Effect of Bran, Am. J. Digest. Dis. **8**:298, 1941.

336. Morgan, J. W.: The Harmful Effects of Mineral Oil (Liquid Petrolatum) Purgatives, J. A. M. A. **117**:1335 (Oct. 18) 1941.

337. Felsen, J.: Sigmoidoscopic Diagnosis of Periarteritis Nodosa, Ann. Int. Med. **15**:251, 1941.

The accurate description of the arterial lesions noted in the rectum and the rectosigmoid portion of the colon is excellent.

Gastrointestinal complaints due to various allergic manifestations are reported in detail by Thomas and Wofford [338] on the basis of 134 cases. The vague nature of the symptom complex is one of the distinguishing features, together with the fact that associated allergic manifestations were present in 90 per cent of cases. There was an 84 per cent incidence of familial allergy.

A complete review of the roentgenologic literature for 1940 as it pertains to the digestive tract is presented by Feldman.[339] The article is of particular value to those interested in the subject because of the well arranged bibliography that is appended to the comments on individual articles and serves as an excellent basis for reference.

Greater use is being made of peritoneoscopy as a diagnostic procedure in properly selected cases. Three hundred and fifty observations are reported in three papers by Walker and Playfair,[340] Olim [341] and Garrey.[342] The data presented by these authors justify the use of the procedure and the assertion that it will save many patients the risk and discomfort of an open abdominal exploration. It has been found to be of particular use in the evaluation of gastric and hepatic conditions and in the diagnosis of peritoneal and of pelvic disease. With care adequate biopsy material can be obtained without undue risk. It would seem that this method has now properly been added to other well established procedures as a safe, economical and reasonably accurate means of obtaining information in properly selected cases.

War Medicine.—The importance of gastrointestinal diseases and complaints in the present emergency is discussed in full by Pepper.[343] He presents statistics of diseases encountered among soldiers in the United States Army during the mobilization period from 1917 to 1919 as a basis for a comparison with the expected morbidity and mortality in the present conflict. The most frequent causes of hospitalization in this

338. Thomas, J. W., and Wofford, C. P.: Gastro-Intestinal Allergy: A Review of One Hundred and Thirty-Four Cases, Am. J. Digest. Dis. **8**:311, 1941.

339. Feldman, M.: A Clinical Roentgenological Review of the Literature for 1940, Pertaining to the Digestive Tract, Am. J. Digest. Dis. **8**:279, 1941.

340. Walker, R. M., and Playfair, P. L.: Peritoneoscopy: Report Based on One Hundred and Twenty-Five Cases, Lancet **1**:159, 1942.

341. Olim, C. B.: Peritoneoscopy: Analysis of One Hundred and Fifty Cases, Surgery **10**:391, 1941.

342. Garrey, W. E.: Evaluation of Peritoneoscopy with Particular Reference to Diagnosis of Abdominal Tumors, New England J. Med. **225**:180, 1941.

343. Pepper, O. H. P.: Disease Expectancy in the New Army, War Med. **1**:463 (July) 1941.

group of over 2,250,000 men for definite diseases of the digestive tract are recorded as follows: ulcer of the stomach, 1,201; duodenal ulcer, 884; appendicitis, 21,689; hernia, 35,535; other diseases of the stomach, 29,271; other diseases of the intestines, 54,665; diarrhea, enteritis and colitis, 38,355, and diseases of the liver and the gallbladder, 6,443. As Pepper states, this group is of no mean importance and there is little reason to believe that there will be any lessening in the frequency of peptic ulcer; in fact, there is likely to be a definite increase, if rumors concerning the frequency of this condition in the armed forces of other countries can be believed. He is also correct in the following statement:

> As to the indefinite miscellaneous disorders of the stomach and of the intestines, diarrhea, enteritis and colitis, a marked improvement should be expected, proportionate to the better diet and even more to the more cleanly preparation of food which it is hoped will be the rule in the new Army. This factor is controllable to a great extent. If figures approaching those of the past are permitted to occur, it will be a disgrace. A lower incidence of intestinal infestations can also be part of the expectancy.

Because of the distribution of the armed forces it is to be anticipated, however, that there may be a tremendous increase in the incidence of tropical diseases, including the various forms of dysentery, which, however, should be amenable to successful treatment, as indicated in the earlier part of this review. Because of the magnitude of the problems and strains involved in modern mechanized warfare, it is apparent also that various disorders which are more or less conditioned by varying degrees of nervous strain and by adequacy of diet will be encountered in important numbers. The peptic ulcer problem may be minimized by the proper exclusion of known patients with ulcer from the combat forces. It is inevitable, however, that numerous persons, particularly in the enlisted personnel, will be inducted into service without the discovery of a quiescent ulcer.

The importance of the ulcer problem has been already noted in previous reports appearing in the European literature and is reaffirmed in an article by Urquhart, Singleton and Feasby,[344] who comment on the frequency of duodenal ulcer among the Canadian forces. In the group of cases under discussion by these authors, symptoms of ulcer developed in 90 per cent within the first six months of service in England. In about one third of the cases the patients gave histories of no previous gastric disturbances. In this article there is also an excellent discussion of the incidence of dyspeptic symptoms. An intelligent evaluation of these symptoms made it possible to keep the majority of these "functional dyspeptics" on active duty.

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344. Urquhart, R. W. I.; Singleton, A. C., and Feasby, W. R.: The Peptic Ulcer Problem, Canad. M. A. J. **45**:391, 1941.

A complete discussion concerning the methods of the examination and disposition of persons with gastrointestinal symptoms is presented by Schindler,[345] who considers a large variety of conditions, in addition to gastritis. The author classifies for ultimate disposition and treatment most of the important disorders in an intelligent and comprehensive fashion. In the preparation of his article he has taken advantage of broad clinical experience derived by himself and others during the last war. He stresses the importance of obtaining objective evidence in individual cases, rightly claiming that this is much more important than any "impression" a military surgeon may derive from a careful history. This is particularly true when it is necessary to rule out malingering. He makes a particularly intelligent attempt to evaluate the possible activities that may be permitted to patients suffering from various disorders that may incapacitate them for combat duty.

The Army's nutritional problems are fully discussed by Tobey,[346] with especial attention to measures for situations such as those that arise during tank movements, parachute work and aviation activities. In such forms of mobile combat, concentrated rations are important and are duly considered.

The importance of abdominal distention in the production of annoying or even dangerous symptoms as it relates to the problems of aviation is discussed by Vega [347] and by Collins.[348] The great increase in the volume of gastrointestinal gases at high altitudes may result in a forcing upward of the diaphragm with striking alteration in respiration, associated with a diminution of vital capacity, alveolar oxygen tension and carbon dioxide tension. Respiration approaching that of the Cheyne-Stokes type, according to Vega, may be noted because of undue abdominal distention. An unusual manifestation of such a condition is reported by Collins in a patient with congenital idiopathic dilatation of the colon. This person while flying at 14,000 feet (4,200 meters) experienced considerable abdominal distention, dyspnea and precordial pain, which were relieved when the plane descended to normal barometric levels or when large amounts of flatus were passed.

Visceral injury caused by compression or suction waves set up by the detonation of high explosives on land or at sea is described by

345. Schindler, R.: Gastroenterology in the Army: Methods of Examination and Disposition of Cases, War Med. **2**:263 (March) 1942.

346. Tobey, J. A.: The Army's Nutritional Problems, War Med. **2**:437 (May) 1942.

347. Vega, M. G.: Changes in Respiration and in the Digestive Apparatus at High Altitudes, Medicina, Madrid **9**:162, 1941.

348. Collins, L. H.: Excessive Abdominal Distention at High Altitudes in a Case of Congenital Megacolon (Hirschsprung's Disease), J. A. M. A. **117**: 1012 (Sept. 20) 1941.

Breden and his colleagues.[349] Organisms permeating a contused colon were the cause of pelvic and subphrenic abscesses in 2 patients. Seven patients had severe melena but without serious complications, and 1 patient suffered fatal injury associated with laceration of the ileum and peritonitis due to compression. In the last-mentioned patient section of the ileum showed diffuse hemorrhages in the submucous and subperitoneal layers, which were similar to those discussed in a previous article, as a result of abdominal trauma. In all likelihood, the mechanism involved was quite analogous. In the surviving patients the immediate symptoms of vomiting with blood, diarrhea with melena and testicular pain occurring after sudden compression were not severe. Conservative therapy was advocated.

Massachusetts General Hospital.

349. Breden, N. P.; d'Abreu, A. L., and King, D. P.: Sudden Compression Injuries of Abdomen at Sea, Brit. M. J. **2**:144, 1942.

News and Comment

American Association for the Advancement of Oral Diagnosis.—The annual meeting of the American Association for the Advancement of Oral Diagnosis, which was scheduled to be held November 12 and 13 in Boston, has been canceled and will not be held in 1942.

CORRECTIONS

On page 58 of the article "Stenosis of the Infundibulum" by Drs. Maurice Lev and Sidney Strauss, in the July issue (ARCH. INT. MED. **70**:53, 1942), the second sentence of the section entitled "Comment" should read "When the patient was first seen, ten years before death, a systolic murmur was heard at the base of the heart." Similarly, in the last paragraph under this heading, "the base of the left lung" should read "the base of the heart."

In lines 17 and 21 on page 58, "the P wave in lead II" should read "the second pulmonic sound."

In the article by Dr. Harry D. Leinoff, "Acute Coronary Thrombosis in Industry: I. Direct Nonpenetrating Injuries, with Report of Cases," in the July issue (**70**:33, 1942) lead I in figure 4, on page 47, is upside down and indicates, erroneously, that the T wave was upright, instead of being inverted and coved.

Book Reviews

Arthritis in Modern Practice: The Diagnosis and Management of Rheumatic and Allied Conditions. By Otto Steinbrocker, M.D., with special chapters by John G. Kuhns, M.D., F.A.C.S. Price, $8. Pp. 606, with 321 illustrations. Philadelphia: W. B. Saunders Company, 1941.

The problems of arthritis are receiving greater and greater attention from members of the medical profession throughout the country, as evidenced by organizations for the study of arthritis, by articles in current medical literature and by the recent appearance of several books devoted entirely to the subject of arthritis, of which the volume under review is one. This attention to a crippling and disabling disorder which probably is as responsible as any one disease for physical disability and mental suffering is well warranted. Too long have arthritic patients been pushed from pillar to post because of the unsatisfactory results that have been usually obtained by physicians in the management of them.

This book is prepared by Steinbrocker, chief of the arthritis clinic of Bellevue Hospital, New York, and in addition to the nineteen chapters that he devotes to the subject, there are five chapters on painful feet; posture and exercise; splints and supports; manipulation, treatment and operation, and surgical procedures written by Dr. Kuhns, chief of the orthopedic and surgical service of the Robert Breck Brigham Hospital, Boston.

The senior author has devoted the greatest number of pages, naturally, to rheumatoid arthritis. The chapter on this form of arthritis is a clear, concise, authoritative statement of the most frequent cause of disabling joint injuries. It is to be commended highly. The senior author, incidentally, devotes some pages to gold therapy but refuses to commit himself as to the efficacy of this type of treatment.

The succeeding chapters have to do with other types of arthritis, such as hypertrophic arthritis, gout and infectious arthritis. He devotes chapters to painful shoulder, backache, sciatica and other conditions with which a person who is treating arthritis should be familiar, as well as to physical therapy.

This book compares favorably indeed with any and all books on arthritis. It can be recommended. It is well printed, and the numerous illustrations, on the whole, are clear. Altogether, it is pleasing in appearance.

Diseases of Metabolism. Edited by Garfield G. Duncan, M.D., Associate Professor of Medicine, Jefferson Medical College. Price, $12. Pp. 985, fully illustrated, with 7 plates in color. Philadelphia: W. B. Saunders Company, 1942.

The scope of this book is contained in the editor's definition of metabolism—"Metabolism is the sum total of tissue activity as considered in terms of physicochemical changes associated with and regulated by the availability, utilization and disposal of protein, fat, carbohydrate, vitamins, minerals, water and the influences which the endocrines exert on these processes."

To present the fundamental knowledge of metabolism, namely, its physiology, physicochemistry and pathologic physiology; to apply this knowledge to the explanation of diseases of metabolism, and to outline a rational basis for the treatment of these diseases is no mean task.

A brief foreword by Sir Frederick Banting was epically enough received by the editor but a few days before Sir Frederick's untimely death.

The editor has wisely chosen a group of outstanding authorities to assist him. Carbohydrate Metabolism is presented by C. N. H. Long; Protein and Lipid Metabolism, by Abraham White; Mineral Metabolism and Melituria, by Abraham

Cantarow; Water Balance in Health and in Disease, by John P. Peters; Nutritional and Metabolic Aspects of Disorders of the Blood, by Leandro M. Tocantins; Vitamins and Avitaminoses, by Tom D. Spies and Hugh R. Butt; Undernutrition, by L. H. Newburgh; Obesity, by Frank A. Evans; Xanthomatoses, by Edward Mason, and Gout, by Walter Bauer and Friedrich Klemperer. The editor, Garfield G. Duncan, covers Hyperinsulinism, Diabetes Insipidus and Diabetes Mellitus.

The style of each author is uniformly excellent. As the advances in the fundamentals of metabolism have been so revolutionary in the last fifteen years, no medical student, general practitioner or internist could but profit immeasurably by reading this book. The reviewer is willing to predict that the book will become a classic in its field.

Religion in Illness and Health. By Carroll A. Wise. Price, $2.50. Pp. 279. New York: Harper & Brothers, 1942.

Dr. Wise has formulated an approach to religion that embodies and brings to articulate expression many of the ideas implicit in religious teachings, regardless of individual creed. Because of this, his book satisfies a need which many persons had long felt but which had remained unsatisfied because of inability to give it overt expression in words. It is a strange experience to see the fundamental principles of religious teachings expressed in the terminology and concepts of psychiatry, psychology and psychoanalysis; yet this is the unique contribution of the book—a contribution which renders it of particular value and interest to professional groups.

Although the word psychobiology is never used by the author, an exposition of the "organismic approach" is given in Chapter IV, in which the concepts presented are essentially the concepts of psychobiology.

Despite some awkwardness of style and organization the author shows an insight into human behavior that can come only from broad psychiatric and psychologic training and experience. Yet one of the strongest points in the book is Dr. Wise's development of his concept of the role of the clergyman in dealing with problems of mental health. He believes that the clergyman's psychiatric training enables him to define his own sphere of activity as one distinct and different from that of the psychiatrist, but one requiring whole-hearted cooperation with the psychiatrist in the interest of the patient's mental health and well-being.

From Witchcraft to Chemotherapy: The Linacre Lecture 1941. By Sir Walter Langdon-Brown. Price, $0.60. Pp. 60. London: Cambridge University Press, 1942.

This scholarly and entertaining essay would only be spoiled by any attempt at a critical review. It is full of interest to the medically trained man and to the lay reader and can be unreservedly recommended to both as conforming to the best ideal of English medical essays.

Synopsis of Materia Medica, Toxicology and Pharmacology. By Forrest Ramon Davison. Second edition. Price, fabrikoid, $5.75. Pp. 695, with 45 illustrations. St. Louis: C. V. Mosby Company, 1942.

The second edition of Dr. Davison's well known book is much like the first edition, although important additions and deletions have been made. The material on the sulfanilamide drugs has necessarily been enlarged. This book is useful for desk reference.